A.M.A. Archives of
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VOLUME 56 NUMBER 5

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The Relation of Horizontal Saccadic and Vergence Movements
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Refractive Changes in Normal Young Men — *Edward A. Hynes*

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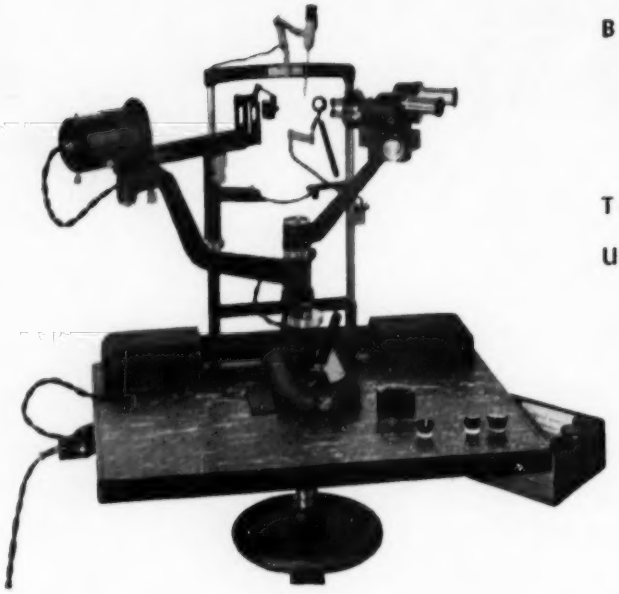

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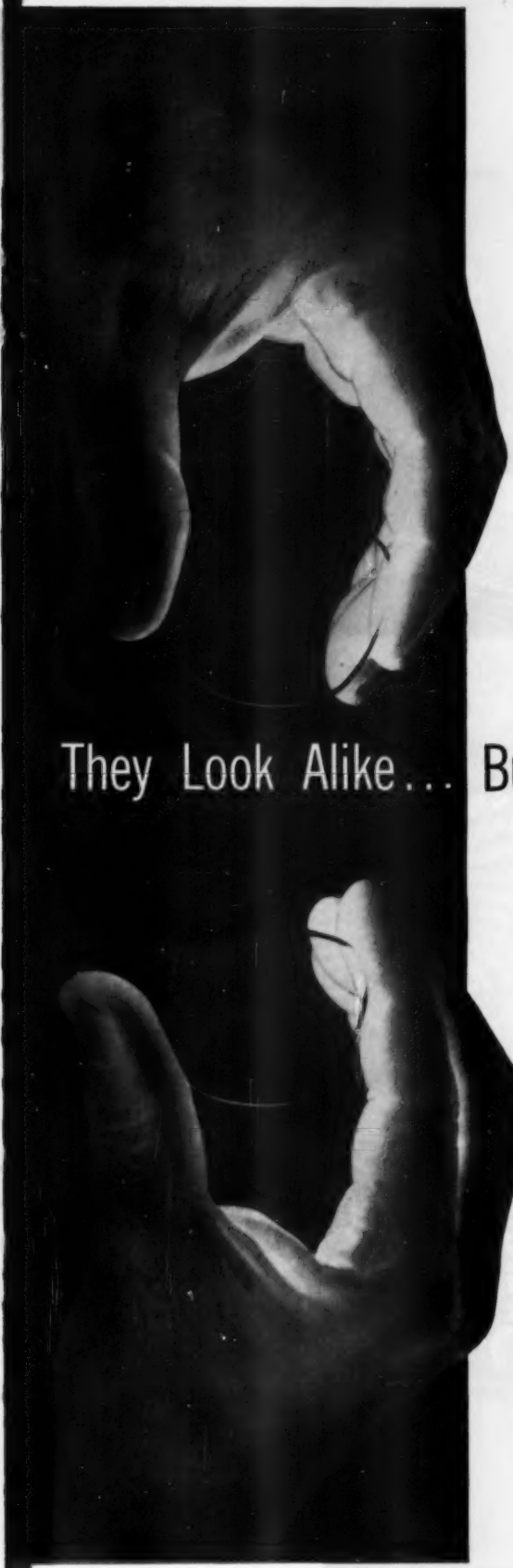

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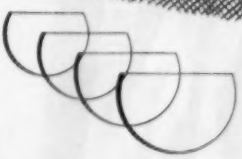

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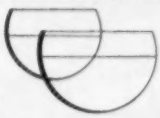

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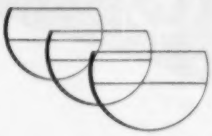

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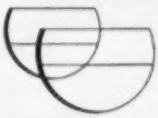

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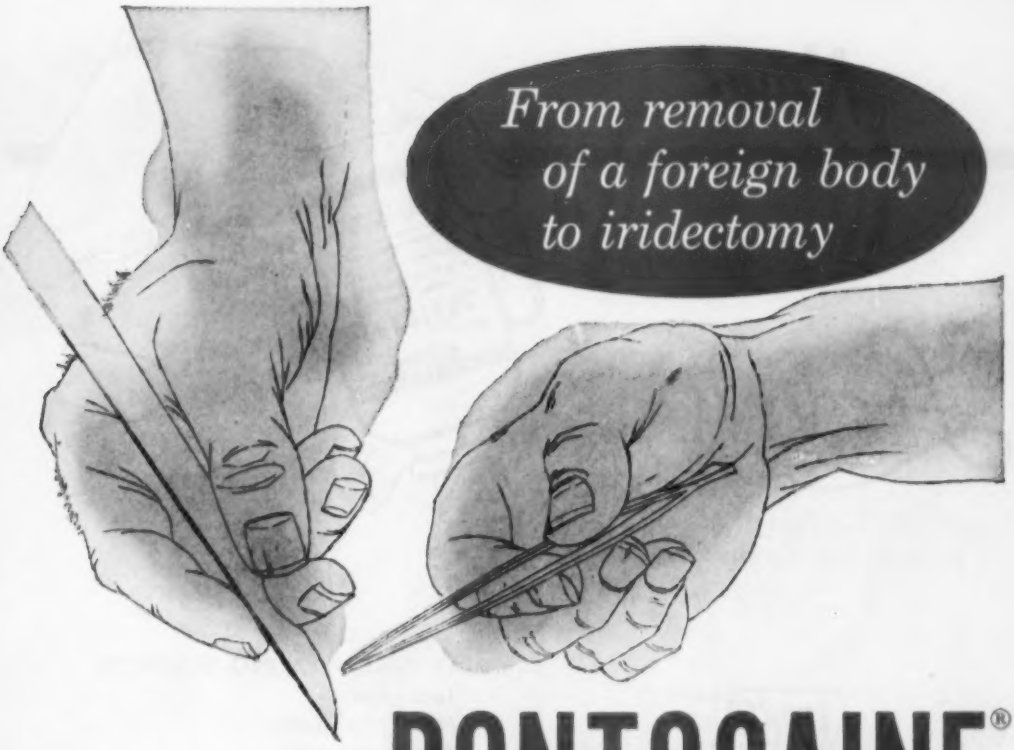

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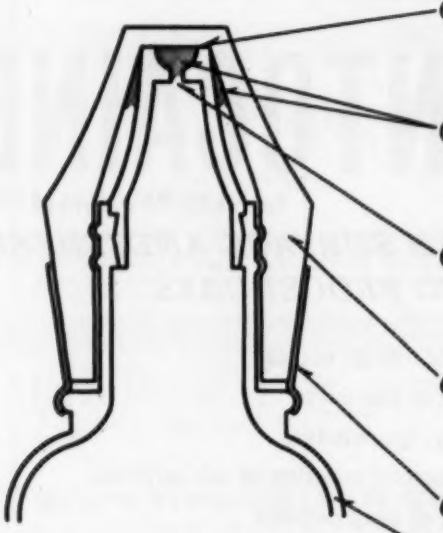

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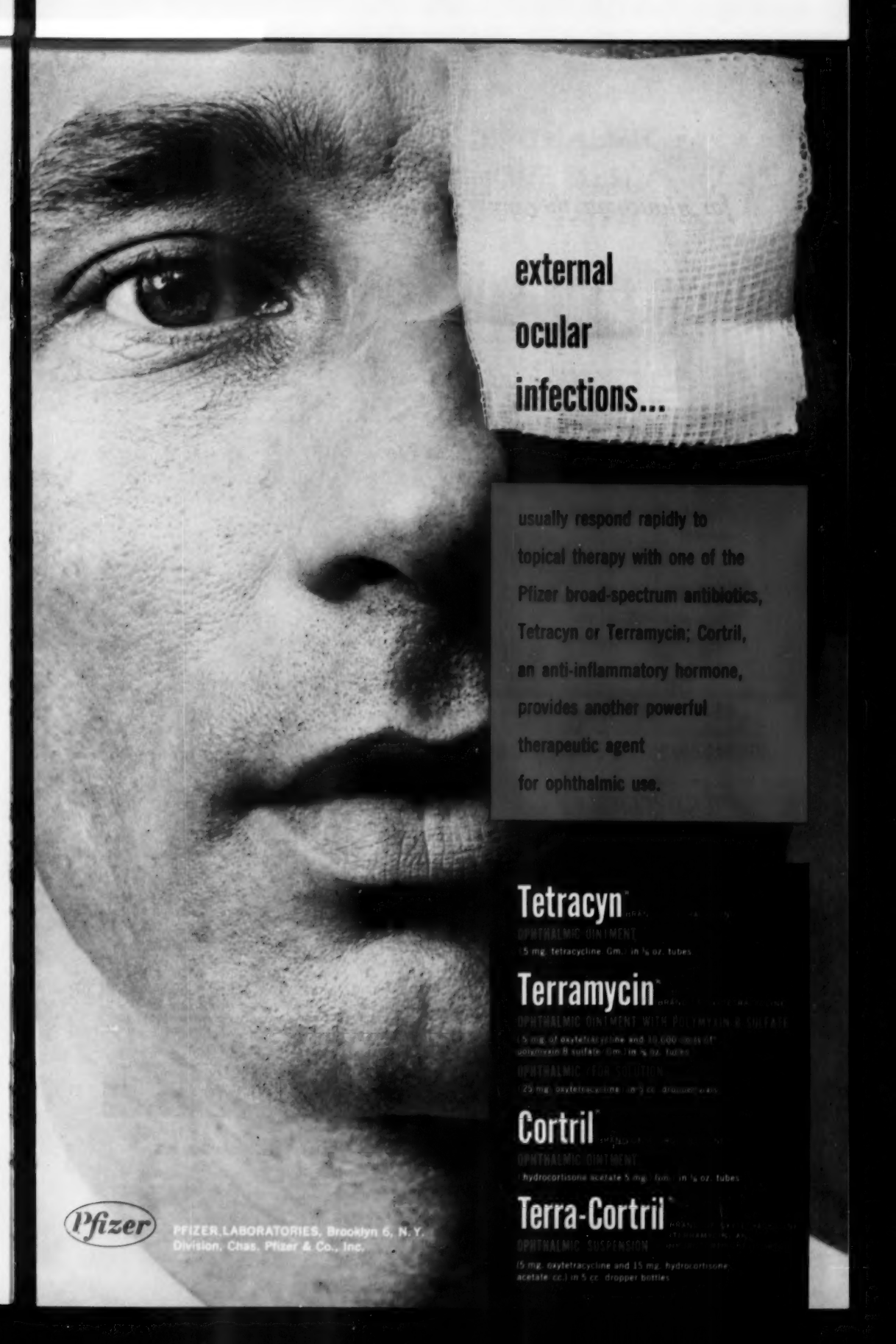
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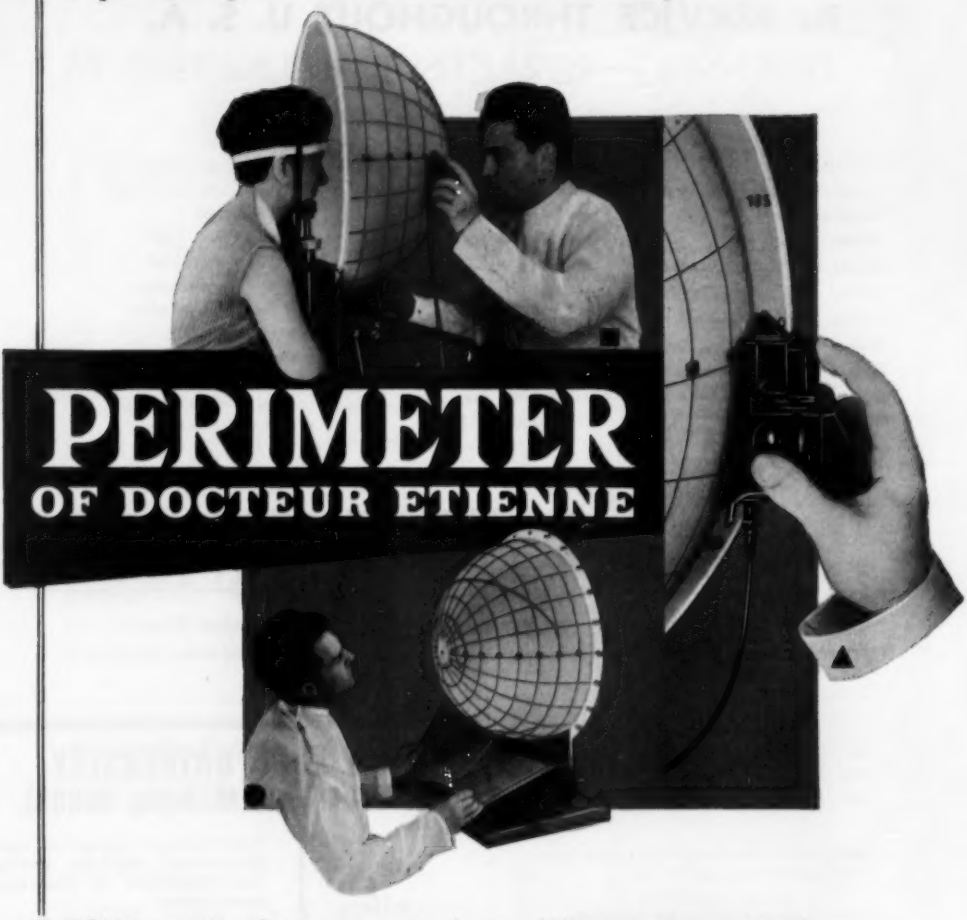

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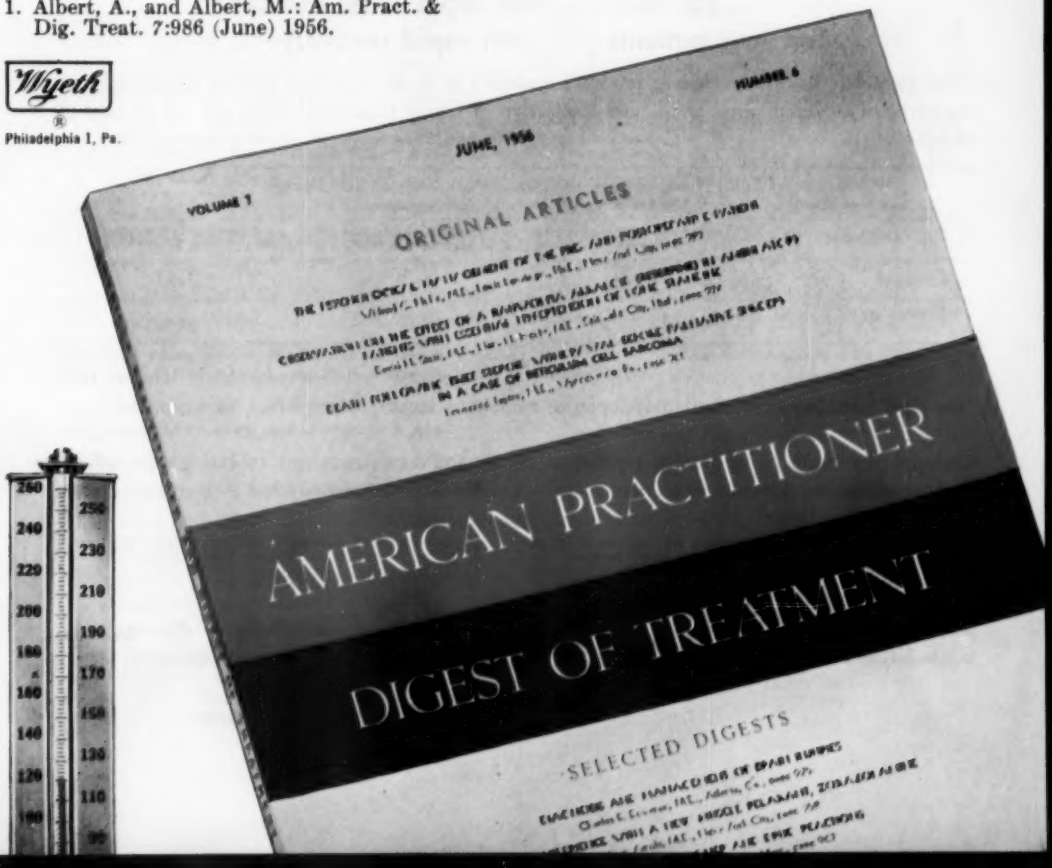

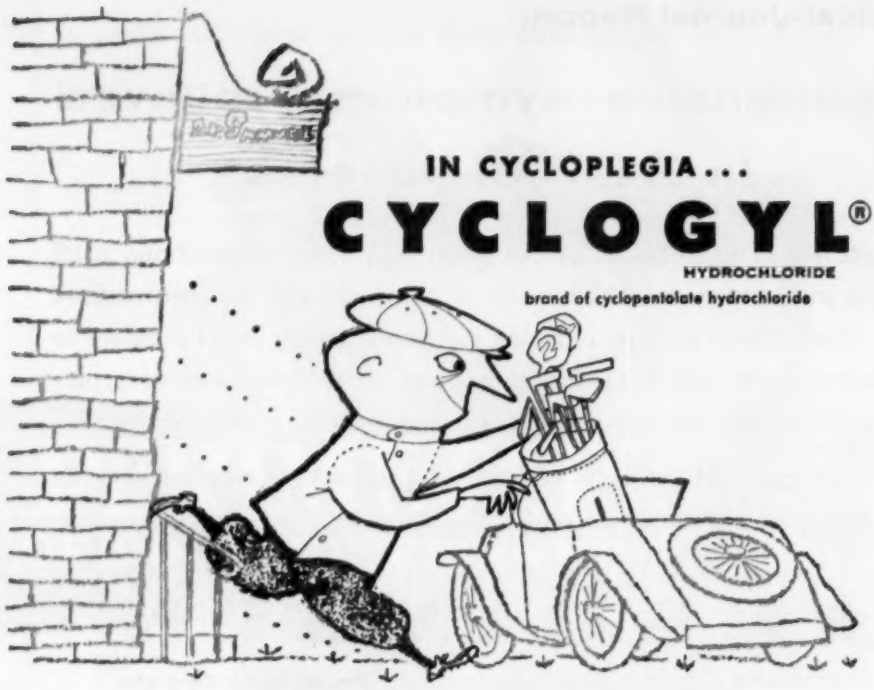

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1. Gordon, D. M., and Ehrenberg, M. H.: Am. J. Ophth. 38:831 (Dec.) 1954.

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Ocular Wound Healing with Particular Reference to the Cataract Incision

JOHN H. DUNNINGTON, M.D., New York

This opportunity to honor the memory of Sir William Bowman is a great privilege. No physician need be reminded of his brilliant achievements. We, ophthalomologists, like to think of him as belonging only to us, but we must not forget his many original contributions to general medicine. It was he who first described the microscopic structure of muscle and of kidney and laid many of the foundations of histology. The manifold accomplishments of this genius belie description so ophthalmology is indeed fortunate he bestowed upon it a lion's share of his boundless enthusiasm and tireless energy. Sir William Bowman [1] in his inaugural address as first president of this society praised his predecessors in words which best describe the very position he himself now holds. On that occasion he said "Honour to those men who have been foremost in discerning the true lines of progress, and in pursuing them for our common benefit and profit—benefactors of mankind, to be one day recognized by all." To acknowledge by this lecture ophthalmology's debt to this great scientist is a challenge I have approached with genuine pleasure and profound humility.

In the eighteenth century Daviel reported the successful removal of a cataract through an incision in the lower part of the cornea. Although this new operation was not accepted immediately, as its advantages became apparent more and more interest was directed to the incision. In those preanesthetic days the accessibility of the lower part of the globe constituted a strong argument in favour of placing the incision below the horizontal meridian. To encourage smooth healing great precautions were taken to prevent the lower lid from getting between the lips of the wound. Surgeons soon recognized the importance of an opening of ample size and the possibility of enlarging the incision with scissors. Their astuteness is exemplified by Ware's (1793)[2] discussion of the following causes of failure in cataract extraction: (1) small incision; (2) injury to the iris; (3) loss of vitreous; (4) retention of part of the cataract. The evolution of the present-day procedure has been a gradual one, highlighted by many changes such as the introduction of

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anesthesia and akinesia, the use of corneoscleral sutures, and the intracapsular extraction. Although the incidence of failure has been greatly reduced by the various technical advances, we must remain ever conscious of Bischoff's (1793)[3] advice that "minutiae which though they at first sight appear insignificant yet are known to contribute essentially to the expedition and completion of the cure." It is the purpose of this presentation to reemphasize the soundness of his teaching by showing the significant role minor imperfections in wound healing still play in the production of serious sequelae.

Part I. Normal Healing

Modern Concepts of Healing.—Recent experimental studies and clinical observations upon the mechanisms of normal repair of a cataract incision have only confirmed many of the findings of earlier histologists. The mechanical slide of adjacent epithelial cells over a denuded area was observed by Ranvier (1896),[4] the role of mitotic activity in the healing of epithelial lesions by Weinstein (1903),[5] the stromal repair effected through invasion of spindle-like cells by Salzer (1909),[6] and the regeneration of Descemet's membrane through endothelial proliferation by Weinstein (1903).[5] In 1907 Henderson[7] presented "A Histological Study of the Normal Healing of Wounds After Cataract Extraction," which is remarkable for its lucidity as well as for its many valuable conclusions. This author recognized that when there is faulty apposition of a corneal wound, epithelium may cover its surfaces and extend into the anterior chamber, producing an intractable glaucoma. He also showed histological specimens illustrating the relatively inactive role the sclera plays in the repair of a limbal wound and the effect incarcerated tissues have upon wound healing.

Within recent years additional information on the healing of corneal wounds has appeared. My experiments[8] as well as those of Ashton and Cook[9] have confirmed the earlier observations that the primary closure of any corneal incision is effected through swelling of the corneal lamellæ produced in large part by imbibition of aqueous humor. After this central contact has been established, the stromal surfaces soon become agglutinated and within three or four days keratoblastic proliferation is observed and stromal healing begins. In the initial stages the normal retractivity of the tissues produces separation of the anterior and posterior edges of the wound. The surface epithelium, however, rapidly covers the denuded anterior area by a sliding inward of the cells along the edges of the wound and later by their mitotic proliferation, so that usually by the end of the second day the surface is completely blanketed. This anterior epithelial triangle is gradually pushed out of the lips of the wound by the proliferation of keratoblasts. In the presence of a conjunctival flap the anterior gaping surface is soon filled with episcleral fibrovascular tissue, the amount and depth of which is determined by the degree of separation of the wound edges. As stromal healing progresses the plug of fibrous tissue becomes smaller by being pushed toward the anterior chamber.

The gaping posterior portion of the wound does not participate in the immediate repair. Earlier investigators reported that this triangle rapidly filled with fibrin. This finding was recorded by both Weinstein[5] and Tooke[10] working with rabbits. Henderson[7] and Collins[11] believed the posterior part of the incision became closed early in the repair. However, in the more recent descriptions by Maggiore,[12] Purtscher,[13] and Kara[14] this fibrinous plug was not mentioned; nor

did I find it in my histological specimens. It is true that in the illustrations of these later writers and in many of my microscopic sections there is a small amount of exudate at the apex of the posterior triangle. This coagulum appears either to be due to seepage from the adjacent corneal stroma or, if a conjunctival flap is present, to arise from the episcleral tissue. In any case the posterior part of the wound is not an active participant in the early healing process. By the end of a week, when stromal proliferation has become well established, endothelial proliferation begins to bridge the defect produced by retraction and inward curling of the cut edges of Descemet's membrane.

The slowness with which ocular incisions become completely healed was shown by Purtscher's [13] microscopic studies of two eyes removed 14 and 15 days after cataract extraction. In both specimens the conjunctival flap was firmly closed by young scar tissue but the corneal healing was still incomplete and limited to the anterior part of the wound. Maggiore,[12] in an extensive study of corneal wounds, recorded similar findings after 10 to 12 days, and concluded that it takes from two to three months for a cataract incision to heal completely. In confirming these earlier observations I [8] have shown that, although cataract incisions on monkeys appear well healed within two weeks, there is microscopic evidence of defective healing posteriorly (Fig. 1).

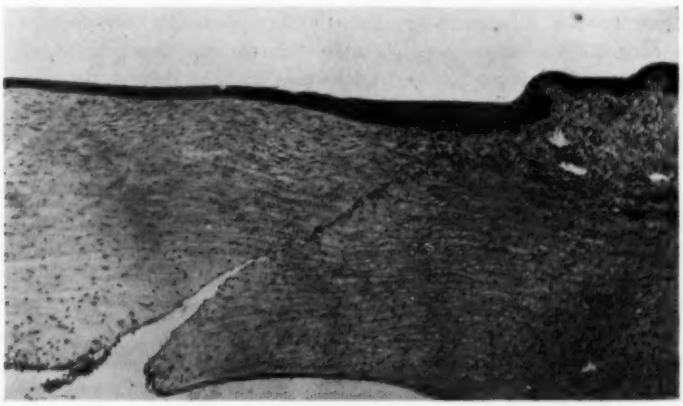

Fig. 1.—Section af an eye of a monkey two weeks after operation, showing firm healing anteriorly and delayed healing posteriorly.

Recently Gliedman and Karlson,[15] using a tensiometer, studied in cats the breaking point of limbal incisions made without a conjunctival flap and closed with 000000 Atraumatic nonabsorbable surgical (silk) sutures. They found the tensile strength of these wounds in the immediate postoperative period to be 6.5% that of the previously undisturbed limbal tissue. After a lag period of three days the strength rose gradually until on the ninth postoperative day it was 15.4% of normal. By the 14th day the strength had become 34% that of undisturbed limbal tissue. Thereafter followed a plateau, with a gain of about 1% a week. Six months postoperatively the tensile strength was only 62% of normal tissue. Gliedman and Karlson by correlating these findings with histological studies showed the lag phase corresponded to the histologically observed exudative phase and the subsequent rise in tensile strength occurred simultaneously with fibroblastic and vascular proliferation. The accelerated increase in tensile strength was thought to take

place when fibroblasts infiltrated the innermost portion of the limbal wound and some contraction of the wound occurred. These findings corroborate my histological observations that the healing of limbal incisions is not complete for at least two months.

Influence of Sutures.—To attain normal healing it is essential for the surfaces of any wound to lie in apposition without distortion and without intervention of surrounding tissues. In most incisions sutures are used not to force together gaping surfaces but to reinforce tissues already in proper apposition. The technique of suturing as well as the material used may vary, but to insure the best effect the basic principles outlined by Howes and his co-workers * and others † must be followed. Foremost in importance is the recognition that the immediate strength of a sutured wound is not dependent upon the tensile strength of the suture employed but rather upon the holding power of the tissues themselves. Therefore it is futile to use a suture with a tensile strength greater than that of the tissues into which it is inserted. Furthermore, even though sutures placed in tissues lose between 40% and 50% of their dry thread strength through wetting and knotting, most of them retain a functionating strength far in excess of the tensile strength of the tissues.[18] Since all sutures by inciting foreign-body reaction devitalize the tissues, their presence lowers the tensile strength of the structures in their immediate vicinity. For this reason the number of sutures used should be no greater than necessary to maintain apposition. The degree of tissue response incited by a suture depends upon its size, the depth at which it is inserted, the amount of tissue included in the bite, and the tightness with which it is tied, as well as upon the material of which it is made. Howes,‡ in his studies of the reactions produced by sutures, demonstrated that one of large size and great tensile strength is often not so effective as a finer, less strong one because the large suture by producing a severe tissue response weakens the wound edges to such an extent that the holding power of the tissues is inadequate to prevent it from cutting out. If a deeply inserted suture which of necessity includes more tissue in its bite is tied tightly, the involved tissue tends to become necrotic. Therefore, unless the suture is removed prior to necrosis it will slough out and leave a weakened area in the wound.

Although silk has long been the most popular suture material the use of absorbable surgical (gut) sutures is on the increase. Many former objections to the absorbable material have been overcome through improved manufacturing techniques. The development of finer sizes and standardization of the processes of chromicization and sterilization have led Jenkins, Hrdina, and their co-workers §; Howes,[19] and other investigators ‖ in general surgery to rely more and more upon surgical gut for wound closure. These same refinements have also increased its usefulness in ophthalmic surgery.[27] Inasmuch as silk and surgical gut invoke different responses in the ocular tissues, it is well to review these reactions.¶ When silk is used there is a rapid downgrowth of epithelium along the suture track, and in many instances this groove becomes completely lined within 48 hours. Fibroblastic proliferation is not delayed, round-cell infiltration is mini-

* References 16-19.

† References 20-22.

‡ References 16, 17, and 19.

§ References 23-26.

‖ References 20 and 21.

¶ References 28 and 29.

mal, and at the end of a week the wound adjacent to the suture is healing well. Between the 9th and 12th postoperative days a marked change takes place around the suture. At this time the round-cell invasion becomes extensive and stromal necrosis appears. If the silk suture is not extruded by the end of two weeks, the surrounding area of the wound is composed of necrotic tissue and many polymorphonuclear leucocytes. In the presence of a deeply inserted suture this reaction often invokes the entire thickness of the cornea.

When plain surgical gut is used it is rapidly surrounded by polymorphonuclear leucocytes, and fragmentation of the suture has begun by the third postoperative day. At this time fibroblastic proliferation is not well established and the wound surfaces may separate. If the material is mildly chromicized 000000 surgical gut, a slight polymorphonuclear response occurs during the first 72 hours after operation followed by increasing fibroblastic proliferation from the 4th to 6th days. At the end of the first postoperative week there is an increase in the number of round cells, especially macrophages. It is at this time that definite fragmentation and absorption of the suture is first observed. During the second postoperative week the process continues and is accompanied by increasing vascular reaction in the form of dilation and perivascular cuffing of the episcleral vessels. With either plain or mildly chromicized surgical gut there is no evidence of stromal necrosis or of epithelial invasion. Although the wound appears to be healing satisfactorily by the 14th postoperative day, shreds of suture material may remain for many weeks and act as centers of small granulomas. In the presence of silk initial responses are most promising, but the rapid proliferation of epithelium along the suture track and the late stromal necrosis are unfavorable reactions. The absence of these findings is striking when surgical gut is used, but this material evokes a much greater vascular response than does silk.

Influence of Local and Systemic Measures.—The many recent therapeutic advances make it desirable to consider the effect of some of the newer drugs and hormones upon wound healing. Although most of these studies are still incomplete, findings of clinical significance have been recorded on cortisone, corticotropin (ACTH), and thrombin.

(*a*) Cortisone and Corticotropin: In 1949 Ragan, Grokoest, and Boots[30] reported delayed wound healing in patients receiving cortisone, and later in the year Ragan and other associates # concluded from experimental studies on the rabbit that cortisone at least partially suppresses the formation of granulation tissue. Since this original report many conflicting statements have appeared in the literature. The findings vary with the amount of substance used, the duration of its use, and the nutritional and metabolic state of the subject, as well as with the species of the experimental animal. Most investigators now agree that when administered in adequate amounts to suitatble experimental animals cortisone delays wound healing. Both Zoger (1952)[33] and Lattis and co-workers (1953),[34] having observed a time lag before the effect of cortisone becomes evident, believe it is without influence on the primary exudative phase. It is not yet clear whether the effect upon healing is purely quantitative or also qualitative. Originally Ragan (1949)[31] thought the connective tissue in cortisone-treated animals displayed both types of change and resembled that seen in scorbutic animals. In contrast, Bangham (1951)[35] reported: "Histologically the granulation tissue in the cortisone-treated animal did not differ qualitatively from that of the control, the most strik-

References 31 and 32.

ing difference being quantitative." In 1953 Lattis, Ragan, and their associates [34] found a change in the ground substance and stated: "Metachromasia of the ground substance of injured mesenchymal tissue is generally reduced and its appearance delayed in cortisone-treated animals." These experiments seem to indicate that in addition to the quantitative change there is also alteration in the quality of the ground substance. Although Meadows and Prudden [36] reported a decrease in the proliferation of epithelium in cortisone-treated animals, most observers have found no change in the rate of regeneration of this tissue. Baxter, Schiller, Whiteside, and Straith [37] have suggested that any apparent delay in firm union of the epithelium is caused by lack of support by granulation tissue. The effect of cortisone upon the tensile strength of a wound is also debatable. Howes and his co-workers,[38] Bellingham and his associates,[39] and Bourne [40] independently found a decrease in the tensile strength of wounds in cortisone-treated rabbits, while Cole and his colleagues [41] in their experiments on dogs found this hormone exerts no effect on the healing of abdominal wounds. Yasuna and his collaborators [42] could detect no difference in the tensile strength of ocular incisions in normal or in cortisone-treated rabbits in spite of the decreased fibroblastic repair noted in the animals receiving the hormone.

The effect of cortisone upon ocular wound healing has not been clearly established. There have been several experimental studies * within the past three to four years which have only served to confirm the excellent work of Ashton and Cook and their colleagues.† These investigators showed that since the subconjunctival or topical administration of cortisone is as efficacious as the systemic use, its effect upon ocular healing is a local phenomenon. They also demonstrated that apart from differences caused by individual or species variation, the degree of tissue response is determined by the amount of the drug administered. They, as well as Newell and Dixon,[50] observed no change in the rate of regeneration of the corneal epithelium in rabbits when small amounts of cortisone were given subconjunctivally, but retardation did take place when the dosage was increased. Newell and Dixon in their studies of corneal transplants in rabbits found cortisone has no effect upon wound healing for the first 96 hours. After that interval there is a persistence of round cells and a delay in keratoblastic proliferation. All investigators seem to agree that fibroblastic activity in corneal or corneoscleral wounds is delayed by the action of cortisone, but unless the dose is large the inhibition is not complete and eventually wound healing becomes adequate. Under similar conditions in a limbal or scleral wound new blood vessel formation is depressed. Ashton and Cook [9] have reported that the regeneration of endothelium is more readily inhibited than is the reparative process of any other part of the cornea.

Limited investigations have been made upon the effect of corticotropin on wound healing. Baxter, Schiller, and Whiteside (1951)[51] gave 100 mg. of corticotropin daily to five patients and studied the influence of this hormone on wound healing. Their results were inconclusive because delayed healing of skin incisions was observed in some but not all of the patients. Starting three days preoperatively, Alrich, Carter, and Lehman (1951) [52] administered 2.0 mg. of corticotropin daily to albino rats. With this dosage they found no delay in healing, but when 4.0 mg. was given daily they observed a "moderate retardation of healing

* References 43-47.

† References 9, 48, and 49.

in the critical later stages." These experimental findings were not confirmed by Meadows and Prudden [36] or by Schilling and his co-workers.[53] A full discussion of this problem in *Nutrition Reviews* (1954),[54] led to the conclusion that corticotropin in clinical dosage has no appreciable effect upon wound healing.

Reports by Hogan,[55] Henderson and Hollenhorst,[56] and others [57] indicate that successful ocular wound healing does take place in patients receiving corticotropin or cortisone. Nevertheless, the recent investigations of Lattis and his co-workers (1953)[34] and of Savlow and Dunphy (1954)[58] point to the need of caution in the preoperative use of these hormones. The experiments of these authors indicate that cortisone must be given for at least three days preoperatively if its full effect upon wound healing is to be realized. Furthermore, De Kleine [59] believes the influence of cortisone may persist for several weeks after its administration has been stopped. These reports indicate further information is needed to determine the effect the prolonged preoperative use of these hormones will have upon wound healing.

(*b*) Thrombin: Parry and Laszlo,[60] von Grosz,[61] Tassman,‡ Town and Nardoff,[64] and others § have advocated the use of fibrin either to replace sutures or to serve as their adjuvant in the closure of cataract incisions. In a previous communication [28] we have described the histological effects of the combination of thrombin and fibrinogen upon the healing of cataract incisions in the eyes of rhesus monkeys killed at 2, 4, 7, 14, and 21 days postoperatively. These studies showed that in the presence of a conjunctival flap the edges of wounds treated with this substance were not in apposition but were separated by fibrin and subepithelial tissue. When the incision had been made in the cornea, epithelium tended to grow along the surfaces of the wound into the anterior chamber. Fibroblastic repair was not delayed nor was any necrosis observed, and at the end of two weeks the wound appeared well healed with broad fibrous cicatrices. The interference thrombin produces in the apposition of the wound surfaces led us to conclude that it is not the ideal material to insure accurate closure of an ocular wound.

(*c*) Other Substances: From an experimental point of view the influences of ascorbic acid, heparin, and desoxycorticosterone acetate are of special interest. Pirani, Stepto, and Consolazio (1952)[67] have reported accelerated healing of abdominal wounds in guinea-pigs given large doses of ascorbic acid (25.0 mg. daily). Although Schilling and his co-workers (1953)[53] did not find any such increase in the rate of healing, they agree that ascorbic acid is the most important single substance in fibrosis and collagen formation. The inter-relationship of corticotropin, cortisone, and ascorbic acid upon wound healing has not as yet been established, but the studies of Clayton,[68] Bartlett, Jones, and Ryan,‖ and others[71] indicate that these substances do provoke profound and varied responses in the experimental animal.

In 1932 Zakrzewski [72] and later Bick (1949)[73] found that heparin has an inhibiting effect on fibroblastic proliferation. Bick and Haines [74] reported that heparin pellets implanted subconjunctivally in rabbits prevent the closure of trephine openings. Both Vannas [75] and Bick [73] have shown that heparin prolongs the coagulation time of the aqueous of the rabbit. It is possible that the latter's

‡ References 62 and 63.
§ References 65 and 66.
‖ References 69 and 70.

observation on the patency of the trephine openings in heparinized rabbits is due to this phenomenon. A most interesting investigation was undertaken by Binder and Binder [76] upon the healing of linear corneal incisions in rabbits in which the prothrombin time had been reduced to 30% of normal by the administration of ethyl biscoumacetate (Tromexan) and heparin. In these animals the initial exudative phase of wound healing was suppressed, but proliferation of the epithelium occurred at a normal rate. Although the fibroblastic response took place at the usual time, the presence of epithelium along the wound surfaces delayed closure of the incision. As a preliminary investigation I made cataract incisions with a conjunctival flap upon the eyes of six monkeys and deposited pure heparin crystals (approximately 20 mg.) under the flap. The animals were killed at 2, 4, 7, 10, 12, and 14 days postoperatively. Microscopic examination of these eyes failed to reveal any abnormality in healing. The relatively small amount of the drug I used may account for the difference between my findings and those of Binder and Binder.[76]

Desoxycorticosterone acetate, an exceedingly interesting hormonal derivative, is believed to increase the rate of fibroblastic proliferation although it has no effect upon the lag phase of wound healing. Pirani, Stepto, and Sutherland [77] found an excessive amount of granulation tissue present in abdominal incisions in guinea-pigs given this substance. In these wounds there was a relatively greater number of fibroblasts and a larger amount of ground substance. These investigators state that desoxycorticosterone acetate influences immature proliferating connective tissue elements but has little if any effect upon mature fibroblasts. Forano [78] has reported accelerated healing of corneal wounds in rabbits treated with it. These varied reports indicate a need for further investigations of the influences of all these substances upon general and ocular wound healing.

Part II. Abnormal Healing

Wound Rupture.—Many abnormalities of wound healing result from subsequent rupture of the incision. The term as usually employed denotes a sudden separation of the wound, but, as pointed out by Gradle and Sugar,[79] these breaks may be of three degrees: (1) gaping of the wound with edema of the conjunctival flap; (2) rupture of the wound with forcible tearing of the newly formed capillaries and resultant hyphema; (3) rupture of the wound with prolapse of iris. Although these authors dismissed the first and second degrees as unpleasant and not often serious, they may lead to major complications.

Gaping of Wound with Edema of Conjunctival Flap.—With this incomplete healing the eye appears normal in all respects except for a bogginess of the conjunctival flap along the entire length of the incision. While such a wound can hardly be said to have undergone rupture, the edematous conjunctiva does denote seepage of aqueous humor. After about 10 days these wounds usually become flat and firmly healed, but occasionally a filtering cicatrix is the permanent result. It has been possible to demonstrate experimentally that this edema is produced by fluid passing from the anterior chamber through the interstices of the wound.

Experiment: Manometric measurements of the intraocular pressure were made on Rhesus monkeys (Macaca mulatta) under pentobarbital (Nembutal) anesthesia by means of a 30-gauge needle inserted through the cornea into the anterior chamber of the animal's eye. This needle was attached by lead tubing to a Sanborn electromanometer, which in turn was connected to its recording unit.[80] After

the intraocular pressure was registered, it was raised and recordings were made of the rate of its subsequent fall. For this experiment three series of monkeys were used: 1. Eight monkeys (16 eyes) served as controls. 2. Four monkeys (eight eyes) had corneal incisions made with the keratome and enlarged with scissors. A complete iridectomy was done, and the wounds were closed with two appositional corneal sutures of either 000000 black silk or 000000 mildly chromicized surgical gut. 3. In 13 monkeys (26 eyes), after a conjunctival flap had been prepared, a limbal incision with use of the keratome and scissors technique was made and a complete iridectomy was done. The wound was then closed with two appositional corneoscleral sutures and the requisite number of supplementary conjunctival ones. The suture material used was either 000000 black silk or 000000 mildly chromicized surgical gut.

In the eyes of the control series the intraocular pressure after being recorded was raised to 30, 40, 50, 75, and 100 mm. Hg. The pressure was maintained at each of these levels for 20 seconds, and the rate of return to normal was registered. Figure 2 shows the usual rate of fall in the control eyes. When the pressure was maintained for 5 to 10 minutes before release the rate of return to normal was not appreciably influenced.

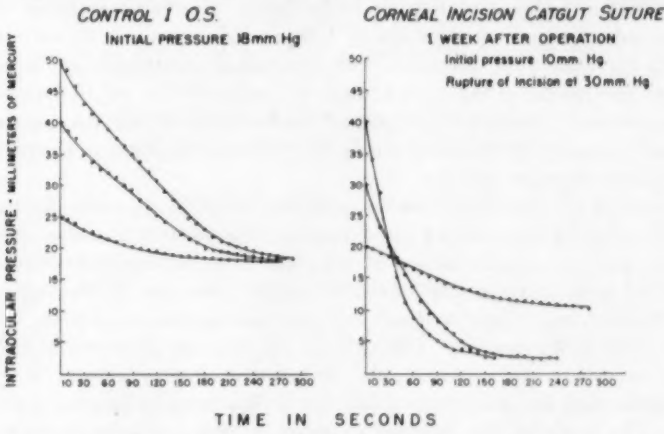
CONTROL I O.S.
INITIAL PRESSURE 18mm Hg
CORNEAL INCISION CATGUT SUTURES
1 WEEK AFTER OPERATION
Initial pressure 10mm Hg
Rupture of incision at 30mm Hg
INTRAOCULAR PRESSURE - MILLIMETERS OF MERCURY
TIME IN SECONDS

Fig. 2.—Graphs showing fall in intraocular pressure in a monkey's eye during control period and after wound rupture.

The second and third series of eyes were tested 4, 7, 11, and 14 days after operation at 30, 40, 50, 75, and 100 mm. Hg for 20 seconds. In all cases except those exhibiting a frank rupture, the fall in the intraocular pressure occurred at a rate similar to that observed in the control series. A few of the animals were killed and the eyes examined histologically. In none was there evidence of wound rupture. On the fourth and seventh post-operative days it was difficult to insert the needle into the anterior chamber without rupturing the wound. When this accident occurred the experiment was terminated and the findings are not included in this report. The criterion arbitrarily selected as indicative of wound rupture was a fall in the intraocular pressure 10 mm. or more per minute greater than the normal rate of decline (Fig. 2).

Four of five eyes with corneal incisions, tested four to seven days after operation, showed evidence of wound rupture when the intraocular pressure was raised to 50 mm. of mercury, whereas only seven of seventeen eyes with limbal incisions

and conjunctival flaps ruptured when tested within the first week after operation. After a lapse of 10 days both the corneal incisions and those with conjunctival flaps showed much less tendency to leak—seepage being noted in only 2 of 12 such eyes. More interesting than the rate with which the elevated pressure returned to normal was the general appearance of these eyes. When the section had been made within the cornea the line of the incision became moist with each rise in intraocular pressure. In eyes with a conjunctival flap and limbal section elevation of the pressure produced an edema of the flap along the entire length of the wound. This edema gradually subsided after the pressure had been released. It is noteworthy that with each rise in intraocular pressure fluid evidently passed through the interstices of the wound without actually reopening the incision. The anterior chamber remained present and of normal depth throughout the entire experiment in all except two eyes. In these eyes with corneal sections four and seven days old, respectively, frank rupture with loss of the anterior chamber occurred. Apparently the seepage of fluid acted as a safety valve against sudden rupture, for even when the wound did break the separation did not occur with sufficient rapidity to produce either prolapse of the iris or hyphema. Furthermore many of these eyes withstood a manometric pressure of 100 mm. of mercury. No attempt could be made to correlate these pressures with tonometric measurements, because the presence of the needle in the cornea made it impossible to use that instrument. Therefore we may conclude that although such edema of the conjunctival flap does denote seepage it is harmless unless the drainage becomes sufficient to alter the depth of the anterior chamber.

Re-formation of Anterior Chamber.—Within recent years much emphasis has been placed upon the role delayed re-formation of the anterior chamber or its subsequent loss plays in the production of glaucoma after cataract extraction. Since the advent of gonioscopy we have become acutely conscious of the angle of the anterior chamber, and Sugar and others ¶ have attempted to correlate its status with that of the ocular tension. Although the incidence of glaucoma is high when peripheral synechiae are extensive, the ocular tension may remain normal. A possible explanation for this apparent paradox is illustrated in the photomicrograph (Fig. 3). The angle of this anterior chamber is open but would appear closed when examined with the gonioscope.

Although delayed re-formation of the anterior chamber is less frequent since the adoption of corneoscleral sutures, its subsequent loss is still common. Kronfield,[85] in an analysis of the hospital records on 749 cases operated upon for cataract, found that in 89% the anterior chamber promptly re-formed and maintained its normal aphakic depth throughout the entire healing period. In 11% (83) the anterior chamber was either slow in re-forming or subsequently became absent. He studied the incidence of glaucoma in this group and found unmistakable evidence of the disease in only 6 of the 83 cases. In the 66 cases in which the re-formation of the anterior chamber had been completed by the sixth postoperative day no cases of glaucoma were recorded. In nine patients with complete re-formation by the seventh or eighth postoperative day only one had glaucoma. Increased ocular tension was present in five of the eight patients in whom the anterior chamber was not permanently reestablished until between 9 and 12 days after operation. Recent analysis of 800 cataract extractions performed on private cases confirm to a large extent these observations of Kronfield (Fig. 4).

¶ References 81-84.

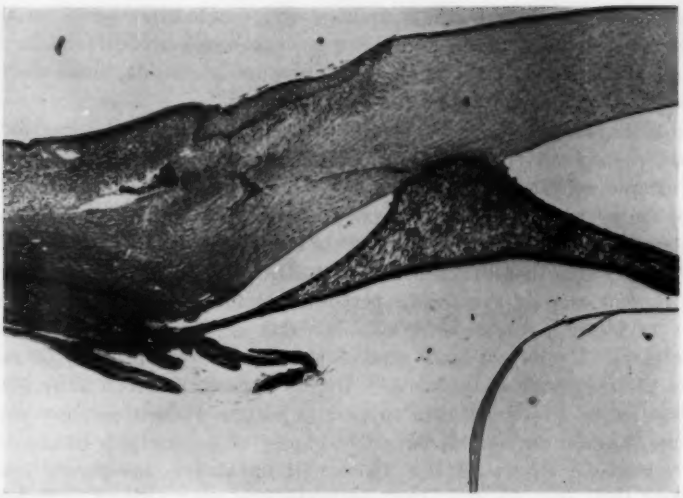

Fig. 3.—Section of an eye of a monkey three months after operation, showing an open angle of the anterior chamber with anteror synechia.

INCIDENCE OF DELAYED REFORMATION OR LATE LOSS OF ANTERIOR CHAMBER

Dunnington	Kronfeld
109 in 800 eyes (13%)	83 in 749 eyes (11%)
Subsequent Glaucoma	
12 in 109 eyes (11%)	6 in 83 eyes (7%)

Figure 4

The cause of delayed re-formation or late loss of the anterior chamber is a debated question. Most authorities concede that this phenomenon always denotes a filtering cicatrix, but others do not agree, because of the occasional inability to demonstrate the exact site of the fistula. Failure to find the opening with the fluorescein test does not establish its absence, for either an intact conjunctival covering or an intermittently open fistula can lead to an erroneous reading. The clinical observation that an absent or shallow anterior chamber often accompanies a minute fistulous opening can be explained on the theory that under these conditions a smaller amount of aqueous humor is actually secreted. No such measurements have been made on humans, but Bellows [86] working with dogs found less aqueous humor was secreted in the presence of a fistula. Thus it would seem that nature by reducing the flow of aqueous humor is attempting to facilitate closure of the opening. Using this reasoning, I sought to lower the incidence of late loss of the anterior chamber by lessening the output of aqueous humor through the systemic administration of acetazoleamide (Diamox). For this experiment 30 cases of cataract extraction were given 500 mg. of acetazoleamide daily from the 3rd to the 14th postoperative days. A control series was obtained by using it only on alternate cases. There were 3 instances of late loss of the anterior chamber among the 30 patients receiving acetazoleamide, and 2 among the 30 untreated

cases. It is interesting that similar findings are recorded by Vail.[87] In his series of 97 cases, 67 of whom received 500 mg. of acetazoleamide from the third to eighth postoperative day, he noted "no difference in the depth of the anterior chamber in either the Diamox or non-Diamox cases."

Wound Rupture with Hyphema.—In spite of the recent advances in surgical technique, postoperative hemorrhage remains an annoying and frequent complication of cataract extraction. In 1933 Vail [88] analysed the data of 24 observers and recorded the average incidence of hyphema as 7.59%, while more recently higher percentages have been reported by Dubois-Poulson and Cragne [89] (21.4%) and Sedan [90] (23.9%). These figures are remarkably close to the findings of my records on 800 cataract extractions performed within the past seven years. The presence of blood in the anterior chamber was noted postoperatively in 20.6% of these cases. My experimental studies indicate the reasons for this recent increase in the frequency of hyphema.[91] I have demonstrated that although corneoscleral sutures do afford sufficient support to prevent sudden complete rupture of the wound they do not abolish the slight gaping of its surfaces produced by the normal retractivity of the tissues. In fact, if the sutures are poorly inserted or tightly tied they may actually cause the wound to gape (Fig. 5). Furthermore,

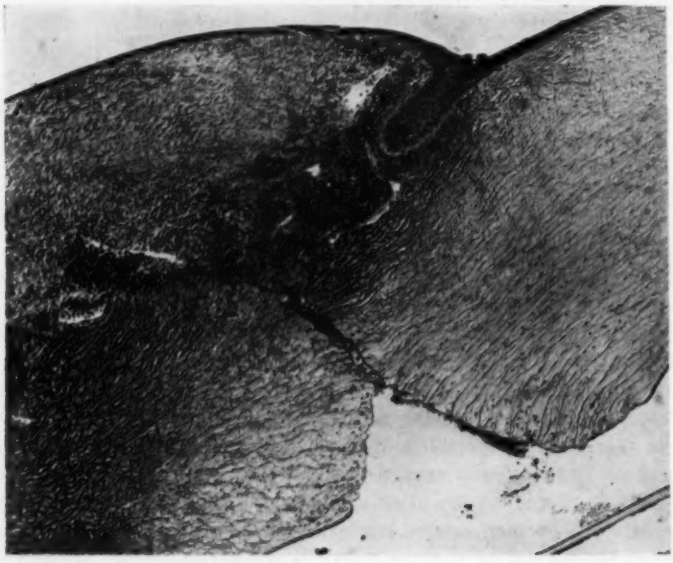

Fig. 5.—Section of an eye of a monkey two weeks after operation, showing gaping of the posterior part of the wound and hyphema produced by a tightly tied suture.

the cellular reactions incited by the sutures themselves often lead to increased vascular response. Mildly chromicized surgical gut provokes a vascular reaction which increases in severity until absorption has been completed. This histological evidence supports the clinical observation that hyphema occurs more frequently and is severer in wounds closed with this material. Of the 800 cataract operations included in our series, in 400 the wounds were closed with 000000 black silk and in 400, with mildly chromicized 000000 surgical gut. The incidence of hyphema in the first group was 17.7%, in contrast to 23.5% in the wounds closed with surgical gut.

An undue stress suddenly applied to the eye with sufficient force to tear the newly formed capillaries in the anterior part of the wound will produce both the separation and the hyphema. The rapid onset of this type of rupture is in sharp contrast to the gradual development of the so-called seeping wound. The source of the pressure which springs the wound is not always clearly established, but all agree it can arise from forcible contraction of the eyelids or of the extraocular muscles. Gasteiger [92] and von Grosz [93] believe that a certain "constitutional moment" occurs during the healing process when any slight external pressure on the eyeball may be sufficient to reopen the wound. Vail [87] thinks this "constitutional moment" coincides with the onset of increased intraocular pressure. He believes the wound is reopened by a temporary glaucoma which arises on the third or fourth day after operation as the result of oversecretion of aqueous humor.

To determine the role this so-called temporary glaucoma plays in the production of hyphema, I decided to keep the ocular tension reduced from the 3rd to the 14th day after operation by administering 500 mg. of acetazoleamide daily to alternate cases in 60 uncomplicated cataract extractions. In the 30 patients receiving acetazoleamide hyphema was noted four times, whereas in the 30 untreated ones it occurred three times. Vail,[87] in a larger series of 67 treated cases, found the incidence to be 16% as compared with 6.6% in 30 untreated cases.

In my experiments to determine the withholding power of sutured cataract incisions 7 and 10 days old, I observed that bleeding did not take place with sudden elevations of the intraocular pressure but did occur when an external force was applied suddenly to the eye. These hemorrhages into the anterior chamber developed regardless of the status of the intraocular pressure. No measurement of the amount of the force was made, but the wounds were easily reopened by external pressure. From these observations one can argue that most hyphemas are precipitated by pressure exerted externally upon the eyeball rather than from separation produced by increased intraocular pressure.

Wound Rupture with Tissue Incarceration.—Sudden rupture of an operative incision is now a rarity, but gradual separation of the surfaces of a wound is not uncommon. In either event tissue incarceration and abnormal healing are to be expected. The significance of this type of defective healing is shown by an analysis of pathological material from the files of the Institute of Ophthalmology of Presbyterian Hospital, New York. For this study microscopic examination was made of 297 globes removed after cataract extraction. Eyes in which other complicating conditions, e. g., perforating injury, could have resulted in enucleation were excluded, as were those from which a congenital cataract had been removed. Although abnormal healing is sometimes associated with such sequelae as sympathetic ophthalmia, endophthalmitis, retinal detachment, and secondary glaucoma, the 126 cases with these diagnosis were not included in this report. The pathological processes induced by faulty wound healing in the other 171 eyes were tabulated as follows:

Tissue incarceration	53 (31.0%)
Stromal proliferation	56 (32.8%)
Epithelial invasion	62 (36.2%)

Because many specimens showed two or more of these findings, the final pathological diagnosis had to be based upon the relative severity of the conditions.

By arbitrarily dividing the cases into two groups I endeavoured to determine the effect corneoscleral sutures have exerted upon the incidence of these complica-

tions. I selected the year 1940 as the dividing line and considered the 53 eyes removed between 1929 and 1941 as having only conjunctival sutures, whereas in the 118 eyes enucleated since 1941 I assumed the wound had been closed with corneoscleral sutures. The findings are shown in Figure 6. The term tissue

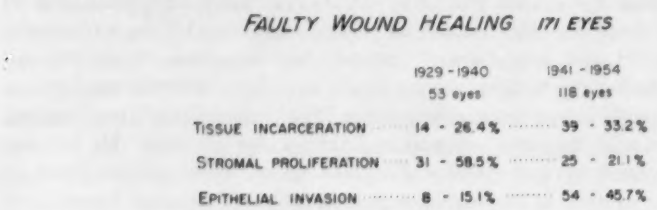

Fig. 6.—Pathological condition responsible for enucleation.

incarceration was used to include all cases with iris, lens, or vitreous entangled in the wound. This complication, which accounted for enucleation in 53 (31%) of the 171 eyes, was not appreciably different in the two groups. Its incidence prior to 1941 was 26.4%, and in the later group it was 33.2%.

"Stromal overgrowth" has been suggested by Duke-Elder [94] to denote the presence of a large amount of fibroblastic-like tissue within the eyeball. The origin of this tissue and the forces exciting its growth have been discussed for many years. Henderson [95] in 1914 described such overgrowth as occurring in poorly apposed limbal incisions with a conjunctival flap. He believed incarcerated iris or lens capsule, by acting as a bridge, allowed the subconjunctival tissue to grow between the lips of the wound and to invade the anterior chamber. Collins [96] in his discussion of this idea stated that proliferation of connective tissue within the eye only occurred in the presence of infective material. However, Swan [97] thinks this reaction arises from the sclera when lens matter, fibrin, or vitreous becomes incarcerated in the wound. Recently Levkoieva,[98] Tichomirov,[99] and Duke-Elder [94] have described this proliferative process in gaping corneal wounds. They believe that in such cases closure is often effected by an exuberant overgrowth which is histologically identical with the processes of regeneration of the substantia propria of the cornea. Its cause is not known, but these authors attribute it to an irritating influence produced by the ocular fluids or by incarcerated tissue. Levkoieva [98] demonstrated the frequency with which this type of healing occurred in badly apposed traumatic corneal wounds covered with conjunctival flaps and urged direct suturing to diminish its incidence.

Of the 171 aphakic globes with faulty wound healing 56 (32.8%) showed evidence of extensive invasion of the eye by this fibroblastic or fibroblastic-like tissue. In these eyes there was often a history of loss of vitreous and incarcerated tissue was usually present. Large amounts of cortex and capsule were frequently found adjacent to the wound and appeared to have acted as the inciting mechanism for proliferation of this tissue. Daniels,[100] working on rabbits, found a similar invasion of the iris by connective tissue from the wound. In my studies on monkeys this type of overgrowth was encountered in poorly apposed wounds with incarceration of iris or lens matter (Fig. 7).

Regardless of the source of this fibroblastic-like tissue, there are three requisites for its production: (1) posterior gaping or over-riding of the wound; (2) incarceration of vitreous, lens matter, or iris in the wound; (3) an irritating stimulant within the eye. Inasmuch as this stromal overgrowth is primarily the result

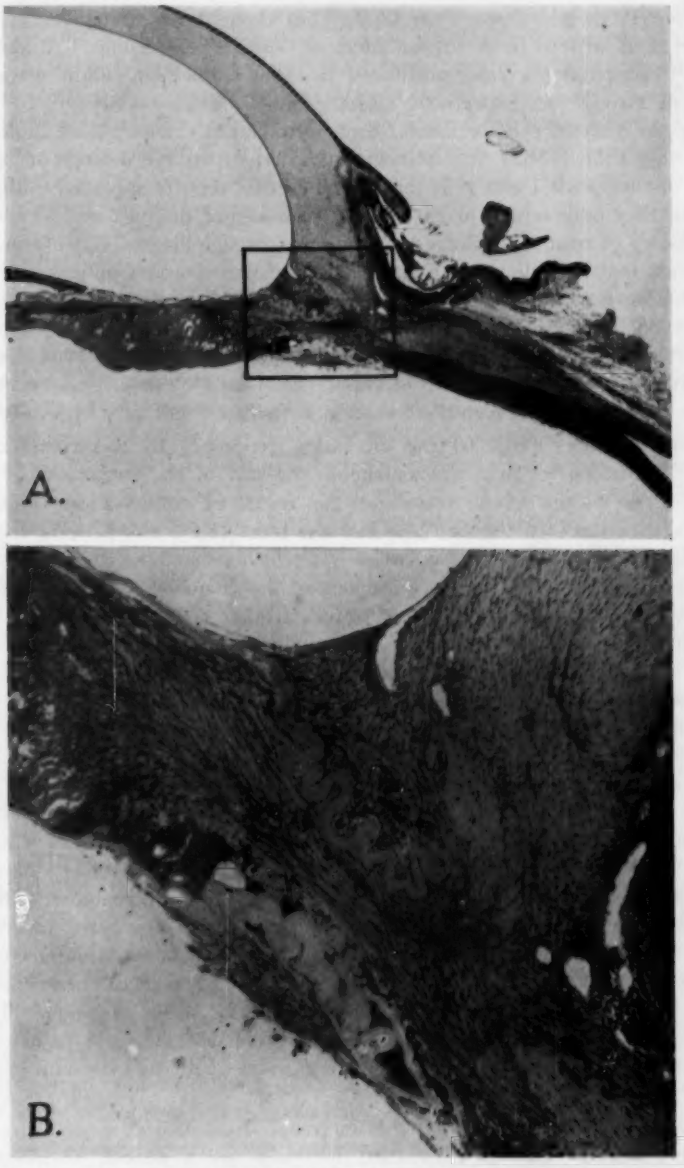

Fig. 7.—*A*, section af an eye of a monkey three months after operation, showing retained lens capsule and stromal overgrowth. *B*, high-power view of inclosed area of *A*.

of gross malposition of the wound, it is not surprising that its incidence has declined from 58.5% to 21.1% since the advent of corneoscleral suturing.

Although recent improvements in wound closure have reduced the incidence of this complication, they have not had the same effect upon epithelial invasion of the anterior chamber. Interest in this baffling and frequent complication has gradually increased ever since its nature was first established by the histopathological

report of Collins and Cross [101] in 1892. They thought this lining of the anterior chamber had arisen from implantation of surface epithelium. A year later Guaita,[102] describing a case, postulated that the epithelium within the eye had grown in through an imperfectly closed wound. Meller (1901),[103] by demonstrating the existence of a fistula, confirmed Guaita's theory and Stalting's [104] earlier suggestion (1885) that epithelium could enter the eye through an operative wound. Between 1901 and 1931 many isolated case reports appeared in the literature, but they only served to confirm the pathological findings and to emphasize the inefficacy of treatment. Corrado [105] in 1931, through his experiments on rabbits, established that epithelization of the anterior chamber occurs only when there is delayed closure of the corneal incision. Perera (1937)[106] found this complication in 4 of 35 aphakic globes subjected to microscopic study. In Theobald and Haas's [107] examination of 75 aphakic eyes enucleated between 1934 and 1945, epithelial ingrowth was present 14 times. Calhoun's [108] description in 1948 of 20 eyes in which he had seen the condition is further proof of its prevalence.

In my statistics (Fig. 6) the increasing frequency of this complication is shown. According to these figures almost one-half of the enucleations done on aphakic eyes within recent years are the result of complications induced by epithelial invasion of the globe. The increase from 15.1% to 45.7% is disturbing, for it has occurred in spite of operative refinements that have materially reduced the over-all number of failures. Conscious of the frequency of this complication, Theobald and Haas [107] urged the use of an adequate conjunctival flap as the best protection against its development. The soundness of this advice cannot be questioned, for ample microscopic evidence is at hand to support their observation that epithelization is more prone to occur in a corneal wound than in a limbal incision with a flap. Although most ophthalmic surgeons use such a conjunctival covering, the incidence of this complication is rising. Furthermore, this increase has occurred during a period when the intracapsular method of extraction has become routine, greater emphasis has been placed upon wound closure, and much more attention has been directed to delayed healing. The experimental studies of Suzuki [109] Perera,[106] and others # have shown that it is difficult to produce viable conjunctival epithelium within the confines of the anterior chamber. Therefore it is hardly tenable to ascribe epithelization of the anterior chamber to incarceration of tags of conjunctiva. Both clinical and experimental observations have shown that epithelium will grow rapidly along the surface of a bit of incarcerated lens capsule. However, with the increasing use of the intracapsular technique this portal of entry is less frequently available. In the aphakic globes I examined histologically, the lens had been removed *in toto* in 36 of the 62 eyes with epithelization of the anterior chamber.

What, then, is responsible for this increase? Inasmuch as most patients with this condition have had an uneventful operation and a smooth immediate postoperative course, neither vitreous loss nor iris prolapse can be implicated in its production. I agree with Vail [111] that "a slowly healing wound, delayed formation of the anterior chamber, leaking aqueous, and fistulization of the wound, are potential precursors" of this conditions. My histological studies have shown that the slough caused by a deeply inserted and tightly tied suture may produce a weakened spot in the wound. If the slough is sufficiently deep or if the suture penetrates into the anterior chamber, aqueous humor will escape. With its loss the iris often

References 105 and 110.

becomes impinged in the wound and delays closure. Thus the stage is set for epithelization of the anterior chamber. I have previously demonstrated that the smooth surface of a silk suture is an ideal track for the epithelium to follow.[28] When the material is chromicized surgical gut the epithelium does not manifest this same invasive quality, because in the process of disintegration the material swells and becomes rough.[29] I find that epithelization of the anterior chamber usually results from a small defect in healing induced either by incarceration of a bit of lens capsule or by improper suturing with silk.

Summary

In reveiwing the modern concepts of healing, particular attention has been directed to the slowness with which the posterior part of a cataract incision becomes firmly united. My histological studies revealing this delay have been substantiated by Gliedman and Karlson's[15] experiments on the tensile strength of limbal wounds. The tissue responses to both absorbable and nonabsorbable sutures are discussed as is the effect of cortisone, corticotropin, thrombin, and heparin upon ocular wound healing. Inasmuch as subsequent rupture of an incision is the cause of most serious complications, this phase of the subject is fully covered. Experimental evidence is presented to show that increased intraocular pressure usually causes fluid to seep through the interstices of a recent wound, whereas pressure applied externally is more prone to produce a sudden rupture. The incidence of delayed re-formation or subsequent loss of the anterior chamber in my series of 800 cataract extractions was 13% and corresponds closely to Kronfeld's[85] finding of 11% in 749 cases. The postoperative administration of acetazoleamide (Diamox) neither cured nor pervented this complication, nor did it influence the incidence of hyphema. Bleeding into the anterior chamber was noted in 20.6% of 800 cataract extractions. When silk was used its incidence was 17.7%, whereas with mildly chromicized surgical gut it was 23.5%. In 171 of the 297 aphakic globes subjected to microscopic study, faulty wound healing was the primary cause of the pathological process responsible for removal of the eye. These conditions were listed as follows: tissue incarceration 31%, stromal proliferation 32.8%, epithelial invasion 36.2%. Corneoscleral sutures have greatly reduced the complications resulting from gross imperfections in wound healing, but they have not done away with tissue incarceration and epithelial invasion of the anterior chamber—conditions frequently produced by slight malposition of the wound. Of particular interest is the increased frequency of epithelial ingrowth—a diagnosis which was made in 45.7% of the aphakic globes enucleated because of faulty wound healing since 1941. Inasmuch as this condition can be produced by improper suturing, attention to such details as depth of the bite, tightness with which the suture is tied, and early removal of the nonabsorbable material should lessen its frequency.

Dr. Ellen F. Regan assisted in the experimental studies and in the preparation of this paper, and Mrs. Marjorie Von Herbulis helped in compiling statistics and references.

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Exophthalmos Due to Pathology in the Orbit or Adjacent Structures

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Exophthalmos is the sign of orbital disease of prime importance. The amount of proptosis may vary considerably in various types of diseases. It may be minimal where the amount of exophthalmos is questionable, or it may be marked so that an unusual appearance of proptosis is present. At times cases have been reported where the eyeball has been displaced anterior to the lids. The determination of exophthalmos may be made by inspection or may be made by measurement.

In considering the differential diagnosis, the question of bilateral and unilateral exophthalmos is important, and it is also important to observe the rate of development of the exophthalmos. Measurement of the exophthalmos may be done by rather simple methods, such as using a millimeter rule and estimating the amount of proptosis of the anterior portion of the cornea beyond the level of the external angular rim of the orbit. However, the Hertle exophthalmometer remains an instrument of choice. Unilateral cases of exophthalmos are of particular interest. Various statistics with regard to groups of cases have been analyzed, and one feature that has been pointed out is this: In cases of unilateral exophthalmos wherein obvious inflammatory disease can be ruled out, a high percentage, in some instances as much as 50% of the cases, have been found to be due to a retro-orbital tumor.

It has been customary to deal with conditions producing exophthalmos under various listings: First, as primary disease, wherein the disease originates within the orbit itself; next, as secondary disease, wherein the disease may originate in associated structures, such as the eyelid, the paranasal sinuses, and the intracranial cavity, and third, as a condition which may represent a metastatic lesion.

Inflammatory Conditions of the Orbit

Acute inflammatory conditions may arise primarily in the orbit, for instance, from a stab wound, but more frequently such infections arise from sources outside the orbit or may be metastatic and will be considered under that category.

Chronic orbital cellulitis may arise either through disease in the orbit or as a periosteitis.

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Pseudotumors of the orbit are an important cause of exophthalmos. The term pseudotumor or inflammatory pseudotumor of the orbit has never been considered a satisfactory designation, but no one has suggested a better name and probably none will be forthcoming until the etiology is established. Such a designation as orbital myositis is unsatisfactory.

The classification which was brought out by Birch-Herschfield a number of years ago still seems to be a satisfactory one. He forms three groups in his classification. In Group 1 are cases in which there is a syndrome of a benign or malignant neoplasm but in which recovery occurs spontaneously or upon the administration of medical treatment. In Group 2 are cases in which the diagnosis of orbital tumor is made clinically but in which no tumor is found when the orbit is explored. In Group 3 are cases in which a retro-orbital tumor is diagnosed clinically and in which one can be found and palpated at operation but in which microscopic examination of removed tissue reveals only chronic inflammatory tissue.

The pathologic picture varies in different reported cases. Reese divides the pathologic picture into four categories, in the first of which there is prominent formation of lymph follicles. In the second, there are focal and perivascular lymphocytic accumulations, usually with muscle involvement. In the third group are conditions in which the chronic inflammation is diffuse throughout the tissue, with little or no destruction and scarring. In the fourth group are those which consist essentially of old fibrous tissue with little inflammatory reaction. The above pathologic grouping is useful in examining various specimens. Whether this represents a different disease process or whether it represents the same disease process in various stages is open to question. It is reasonable to believe, however, that these represent various stages of the same disease process.

A number of these cases have come to operation in the past because of the doubt with regard to the existence of an orbital tumor. The cases in which this is done may show marked improvement after removal of varying amounts of inflammatory tissue. The cases in which surgery is not done slowly show signs of improvement, and frequently the condition ends in enophthalmia.

Vascular Conditions

The following vascular conditions can produce exophthalmos: (1) an aneurysm, (2) an orbital varix, (3) an arteriovenous aneurysm, (4) retro-orbital hemorrhage.

Orbital saccular aneurysms are rare but have been reported. When present they may produce a varying degree of exophthalmos and may be accompanied by a bruit.

An orbital varix causes an interesting clinical phenomenon, namely, transient or intermittent proptosis. The condition consists in dilitation of orbital veins from various causes, probably the most frequent one being trauma. The diagnostic feature of this condition consists of a varying amount of proptosis, which may change in the course of a short time or may change slowly. A characteristic feature is that the proptosis will increase when the head is bent forward and decrease in an upright position. Pressure over the proptosed globe may reduce the amount of exophthalmos, and various changes, such as holding the breath or constriction about the neck, will cause a variation in the exophthalmos. A bruit and pulsation are features of this condition. Most authors recommend con-

servative therapy, but operation has been performed and consists in exposing the involved vessels and isolating them by ligation.

Arteriovenous aneurysms most commonly occur in the cavernous sinus, in which there is a connection between the carotid artery and the cavernous sinus. These may occur spontaneously or may occur as a result of trauma. The spontaneous cases are thought to be due to small congenital aneurysms which rupture because of distention. The traumatic cases may result from head trauma of various types. The outstanding feature of an arteriovenous aneurysm in the cavernous sinus is pulsating exophthalmos. The situation may begin either suddenly or gradually. When it begins suddenly, there may be marked pain, with the rapid production of exophthalmos. When it begins gradually, the exophthalmos may be less prominent, but it may be progressive and associated with a considerable degree of headache. In addition to these signs, a patient may complain of head noise accompanying the pulse beat; the pain may vary considerably; there is loss of vision. A bruit may be heard over the proptosed eye, and a thrill may be transmitted on palpation.

Treatment has consisted of both nonsurgical and surgical methods. Many cases come to surgical treatment, which has consisted in ligation of the common or internal carotid arteries. A rare cause of bilateral exophthalmos has been the thrombosis of a portion of the circle of Willis seen as a traumatic condition in elderly persons.

Hemorrhage as a cause of exophthalmos is usually secondary to trauma wherein proptosis gradually increases with the accumulation of blood behind the globe. If this is not relieved by thrombosis or by drainage, a cyst may form which eventually will require removal.

Tumors

Orbital tumors may be derived from any of the tissue components of the orbit. The great mass of orbital tissue is mesenchymal in origin. The epithelial tissues are represented by the lacrimal gland, and the neural tissues are represented by the optic nerve and the branches of the sensory and motor nerves in their course through the orbit.

Ingalls has reported a review of 216 orbital tumors of various types from the Laboratory of Pathology of the Institute of Ophthalmology of the Presbyterian Hospital in New York. There were 27 different types, but 11 groups represented the commonest tumors. These were the following: (1) angioma, 16.2%; (2) pseudotumor, 13.4%; (3) lymphosarcoma, 10.2%; (4) dermoid cyst, 9.2%; (5) carcinoma from the paranasal sinuses, 7.4%; (6) carcinoma of the lacrimal gland, 6.4%; (7) retinoblastoma, 5.6%; (8) meningioma, 4.6%; (9) melanoma, 4%; (10) neurofibroma, 3.7%; (11) carcinoma secondary to that developing in the eyelids, 3.7%.

Primary Tumors of the Orbit

From the point of view of frequency, a hemangioma is one of the more important types of orbital tumor. It is frequently encapsulated. It may be radiosensitive. It is congenital in origin, usually slow-growing at first, but making its appearance frequently during the latter part of the first decade or during the second decade in life.

Hemangiomas may vary considerably in size, and the symptoms which they produce may vary. Frequently, a considerable amount of exophthalmos or displacement of the eye can result with relatively few other symptoms. They frequently arise within the muscle cone, and when they are outside of the muscle cone they are commonly to the nasal side of the orbit. Occasionally they may increase suddenly in size because of hemorrhage.

Four different types are recognized. First, the capillary type; second, the cavernous type; third, the hemangioendotheliomatous type; fourth, the circoid, or racemose type.

The capillary type consists of numerous fine capillaries with proliferating endothelial cells. It may occur either as an encapsulated or as a nonencapsulated growth.

The cavernous hemangioma is usually encapsulated, irregularly rounded, and composed of large blood spaces.

The hemangioendotheliomata are composed of solid masses of endothelial cells with few or no patent vessels and very small blood channels when these exist. They may or may not be encapsulated. Variations in this type may represent a more malignant type of hemangioma.

The racemose, or circoid, type consists essentially of numerous dilated and tortuous vessels. It may have a sudden onset as a result of hemorrhage in the orbit. Variations in hemangiomas occur, for instance, fibrohemangioma.

Dermoid cysts are developmental tumors. The tumor consists of a cavity lined with epidermal cells and has a wall which contains glands and hair follicles. Such tumors are usually situated in the anterior third of the orbit and are evident early in life. Although these are located in the anterior portion of the orbit, frequently extensions of these cysts may go deeply into the orbit, sometimes nearly to the apex.

Lymphomatoid tumors consist of masses of lymphocytes. There may be a minimal or well-defined follicle formation. They are without inflammatory cells. A report of 65 lymphomatous tumors by Heath indicated that the prognosis could not easily be correlated with the pathologic features. A recent review of a 15-year-old follow-up of 20 patients by McGavic indicated that the prognosis is much better than it has ordinarily been believed to be in the past. Diamond places these tumors in three categories. Category 1 he calls unicentric, without blood changes or other alterations. Category 2 he calls those with beginning generalization but with a reasonable amount of localization in the orbit. Category 3 is the universal one in which patients with leukemia are placed. All of these cases should be treated by radiation. When surgery is done, it may be limited to biopsy in order to verify the diagnosis.

Neurofibromas represent encapsulated growths associated with nerves or to which nerve fibers can be seen to pass in microscopic sections. They represent a part of von Recklinghausen's disease, and it is important to examine cases of unilateral exophthalmos for signs of this disease, particularly café au lait spots.

Plexiform neurofibromas are also associated with von Recklinghausen's disease and represent diffuse changes that may involve a large portion of the orbit. At times the proptosis may be pulsating, because of intermittent pressure transmitted by accompanying vascular changes or because of a dehiscence in the roof of the orbit.

In neurilemmomas, or neurinomas, the histologic picture is characterized by a palisading of the nuclei and fibers. This fasciculation extends through the greater portions of the tumor. The nuclei tend to be elongated and slender. It is a rare tumor.

Glioma of the optic nerve, although an uncommon tumor in the orbit, represents the commonest tumor of the optic nerve. Three-quarters of these occur in the first decade of life. They are congenital in origin. The symptoms consist in gradual exophthalmos in children. The loss of vision is not evident, because the children do not complain of this. It is usually painless. The rotation of the globe is little affected. The rate of growth is very slow. At times there may be changes in the optic nerve, with development of optic atrophy. The site of the origin has been questioned, some believing these originate in or near the chiasm and extend forward rather than originating in the orbit and extending backward.

They can be removed by operation, but sometimes the removal is incomplete, particularly when the growth extends through the optic foramen. Some surgeons recommend combined orbital and intracranial surgery for complete removal of these tumors. However, the literature states that frequently, even in incomplete removal, recurrence does not occur. At times these may be associated with von Recklinghausen's disease.

Verhoff divides the histological features of these tumors into three groups. In the first are those with delicate glial fibers and small cytoplasmic vacuoles. In the second group are those with coarse fibers and large vacuoles giving a myxomatous appearance with circoid spaces similar to cavernous atrophy of the optic nerve. In the third group are those with spindle-shaped cells and coarse fibers.

Meningiomas are much less frequent than are gliomas. They may arise from the sheath of the optic nerve. They frequently are encapsulated. They usually affect adults, the average age of reported cases being in the range of 40 years. They are frequently adherent to surrounding structures and may produce changes in the adjacent bones. They are slow-growing. They may be primary in the orbit and involve the cranial cavity secondarily, or they may be primary in the cranial cavity and involve the orbit secondarily.

These cases frequently show loss of vision and optic atrophy; these symptoms may precede the exophthalmos. There may be irregular changes in the visual fields. The tumor is usually within the muscle cone, and it can give rise to changes in rotation. These tumors arise either from the endothelial cells lining the subdeural space or from cells covering the arachnoid. The histological picture is that of whorls of spindle-shaped endothelial cells usually densely arranged.

A variation of the meningioma is the psammoma, which may arise in connection with the optic nerve. Rarely has it been reported from other portions of the orbit.

Mixed tumors of the lacrimal gland form a definite group. Some of these have been reported under the designation of carcinoma of the lacrimal gland. The name, mixed tumor of the lacrimal gland, is derived from the type of tissues which many of these contain. They do not differ histologically from similar tumors in glands such as the maxillary gland. They frequently make their appearance in adult life and are commonly very slow in growing. They cause a proptosis with the eye pushed down and nasally; because of their slow growth, frequently a considerable amount of displacement may occur without diplopia arising. Some of these are well encapsulated; others are less so. It is generally agreed that the

well-encapsulated and well-differentiated cases respond more favorably to operation, while those with less differentiation do not so respond and require exenteration rather than local excision of the tumor. X-ray diagnosis has helped, and the statement in general has been made that the more malignant tumors of this group will show an enlarged lacrimal gland fossa with increased density of the bone adjacent to the gland. These may be locally removed when they are well encapsulated. However, a certain percentage of these cases show involvement of the bone, and when this is present a more extensive operation is indicated.

The tumor designated as a cylindroma represents a type of mixed tumor of the lacrimal gland in which the epithelial elements predominate so as to form a cylinder appearance within a myxomatous stroma.

A variety of tumors derived from the mesothelial layers have been reported. These include sarcoma, fibroma, and fibrosarcoma; rhabdomyoma, and rhabdomyosarcoma, lipoma, and liposarcoma.

Sarcomata may be seen in children, and under such circumstances frequently are manifested by fairly rapid unilateral exophthalmos, sometimes associated with evidence of hemorrhage. Many of these tumors have a fairly undifferentiated structure, and so they cannot be easily classified.

Rhabdomyoma and rhabdomyosarcoma are rare tumors. The rhabdomyosarcoma in particular is reported to be unusually malignant. The histologic picture in the rhabdomyoma indicates striated muscle cells within the tissue, whereas in the rhabdomyosarcoma the cell picture is that of numerous irregularly shaped cells with nuclei of various size and only an occasional striation evident.

Other mesoblastic tumors are liomyomata, chondroma, and osteomata.

A teratoma represents a developmental tumor. These are rare, and few have been reported in the literature.

Orbital Conditions Secondary to Primary Disease Elsewhere

Orbital disease may be secondary to disease located in the paranasal sinuses, in the cranial cavity, in the lids, in the conjunctiva, and in the globe.

Paranasal sinus disease may lead to orbital cellulitis, either chronic or acute in manifestation. The ethmoid and frontal sinuses are probably the most important ones in this respect, although other sinuses are also involved at times. The mechanism by which the orbital involvement is carried out is either by direct extension through perforations in the very thin bone that separates the sinuses and the orbit or by means of a process of thrombophlebitis and extension of the infection along the vessels.

The formation of the mucocele will produce marked exophthalmos. The usual site of such a tumor-like formation is at the upper inner angle of the orbit, so that the eye is displaced outward and downward. A mucocele consists of a cyst-like degeneration and dilatation of the lining membrane of the sinus. This area enlarges and finally extends into the orbital cavity. Such growths are usually chronic and slowly growing and are usually unassociated with pain, and frequently nasal symptoms are lacking. Rarely, they may be bilateral.

Mucocele of the frontal sinus is probably the commonest and appears at the upper inner angle of the orbit. Mucocele of the ethmoid sinuses is also relatively common and makes its appearance behind the inner portion of the upper lid. Mucocele of other sinuses is relatively less frequent. Treatment of these consists in surgical removal.

Osteomyelitis of the superior maxilla in infants is an important cause of exophthalmos during the first year of life. This condition is consequent upon infection around a dental follicle or may occur as a result of transient bacteriemia from other areas, as for instance, the intestine. The condition can be suspected in cases of unilateral facial swelling with orbital cellulitis in infants.

Cavernous sinus thrombosis is another condition which has a serious prognosis. This is seen very much less frequently now, because of the effectiveness of antibiotics. At one time it was a fairly common condition in the nose and throat services of general hospitals. The frequent exciting cause was a mastoiditis with infection of the cavernous sinus by way of the lateral sinus. The symptoms included a rapid onset with rise in temperature, pain over the eye, progressive exophthalmos, and all the symptoms of a cellulitis with tenderness over the ophthalmic division of the fifth nerve. Frequently papilledema and loss of vision were associated with the other ocular symptoms.

Treatment requires all the methods available and antibiotic drugs in the control of primary as well as the secondary infection. Surgical methods frequently are used.

Malignant tumors involving the nasal pharynx, although rare, may produce orbital complications when they extend into the apex of the orbit. The syndrome of the apex of the orbit indicates involvement of the apex of the petrous bone. The orbital syndrome is present when branches of the third, fourth, fifth, and sixth nerves become involved along with exophthalmos. Diplopia may be an early symptom. Cases of unexplained diplopia associated with facial neuralgia and with swollen lymph nodes should lead one to investigate the possibility of a retropharyngeal tumor.

Meningiomas involving the ridge of the sphenoid bone may give rise to a slowly progressive, painless, and nonpulsating exophthalmos. This will be related to lack of involvement of the globe, with normal vision, fields, and eyegrounds. There tends to be an appearance of suprazygomatic fullness, and x-ray findings indicate hyperostosis of the sphenoidal ridge. These occur most frequently in women of middle age and, curiously enough, have been more frequently noted on the left side.

Carcinoma of the eyelids may involve the orbit. It may be either basal-cell or squamous-cell in type. There may be a tendency for such tumors to extend into the orbit before unusual damage to the lid is evident. An early sign of such extension is limitation of ocular rotations and diplopia as a result of infiltration of the orbit with involvement of the ocular muscles.

Carcinoma of the nasal sinuses may rarely involve the orbit, the antrum and the ethmoidal cells being the most frequent site of such invasion. Occasionally, one of the early symptoms of such involvement is exophthalmos before there is other clinical evidence of the primary involvement in the nasal accessory sinus.

Occasionally, malignant melanoma or melanosarcoma that is primary in the conjunctiva may extend into the orbit and extensive melanomatous growths produce exophthalmos with limitation of rotation.

Involvement of the orbit by an intraocular tumor is possible secondary either to malignant melanoma or to retinoblastoma of the eye. Sometimes such orbital involvement, particularly in cases of malignant melanoma, may be evident before the intraocular tumor has grown extensively.

Metastatic Involvement of the Orbit

The orbit may be involved by metastatic growth of carcinoma, the most frequent primary sites being the breast, stomach, and prostate. Such metastatic involvement leads to proptosis and limitation of rotation and some edema and fullness of the eyelids. Some authors have noted that inflammatory signs associated with metastatic carcinoma may be extensive. Samuels has noted that metastatic carcinoma of the orbit is only one-fifth as frequent as metastatic involvement of the globe.

Metastatic neuroblastoma of the orbit usually arises from a primary growth in the adrenal medulla. When the orbit is involved, the tumor is the Hutchinson type and is accompanied by exophthalmos, ecchymosis of the lids, a tendency to hydrocephalis, papilledema, and cachexia. It arises in children, usually under 10 years of age, commonly only 2 or 3 years of age.

Finally, it should be mentioned that after enucleation recurrent growths may occur in the orbit and at times a so-called amputation neuroma may develop in the orbit. This may account for persistent pain in the orbit following enucleation, and when such a condition is evident the neuroma should be excised.

Endocrine Aspects of Exophthalmos

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This discussion will be limited to the unique constellation of ophthalmopathic phenomena in which exophthalmos is only one of several manifestations and which has been known variously as malignant or progressive exophthalmos, hyperophthalmopathic Graves' disease, exophthalmic ophthalmoplegia, and the infiltrative ophthalmopathy of Graves' disease. It is usually accompanied by hyperthyroidism but may occur in euthyroid persons or occasionally in patients who are in a hypothyroid state throughout. Milder variants of the syndrome have even been described in Cushing's disease. After more than a century of fruitless speculation concerning its etiology and pathogenesis, interest began to center on the adenohypophysis as an important factor about 20 years ago, and in 1944 the nosological concept of Mulvany [1] further influenced this trend of thought. This concept divided exophthalmos into thyrotoxic and thyrotropic types. The former (thyrotoxic) included the milder syndromes manifested chiefly by exophthalmos, lid retraction, and thinning of the extrinsic muscles; enjoyed a favorable prognosis, and was believed to be due directly to the accompanying hyperthyroidism. The latter (thyrotropic) represented a more serious disorder, accompanied by edema and congestive phenomena in the lids, conjunctivae, and orbital tissues, with swelling of the extrinsic muscles and a tendency to progression; hyperthyroidism was mild or absent, and the etiology was ascribed to the adenohypophysis. Today this dualistic concept has been generally replaced by a unitarian view which regards these variations as possessing a common etiology and differing quantitatively rather than qualitatively, and the terms "thyrotoxic" and "thyrotropic" have been largely abandoned. We may therefore conveniently think of endocrine exophthalmos as a spectrum ranging from the mild, static, or reversible forms to the most severely progressive, in which vision may be lost from several causes.

In the full-blown picture the findings include proptosis, edema and pigmentation of the lids, conjunctival injection and chemosis, enlargement of the lacrymal glands, swelling of the extrinsic muscles due to edema and infiltration with lymphocytes and phagocytic cells containing fat droplets, and increased volume of the orbital contents resulting from edema, cellular infiltration, increased fat deposits, and obstruction to venous and lymphatic drainage. The onset is variable. It may precede or follow the appearance of hyperthyroidism, occur without any evidence of thyroid dysfunction, or begin after the spontaneous or induced remission of hyperthyroidism, particularly if the latter has been abrupt. It is sometimes accompanied by curious localized myxedematous changes in the pretibial area, and myxoid infiltrates (possibly hyaluronic acid complexes) have also been

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described in the orbit. The clinical course is likewise variable, and spontaneous arrest or regression may render the evaluation of therapy difficult. In progressive cases varying degrees of immobilization of the globe may occur, often first manifested by limitation of upward gaze, and diplopia is a common symptom. Later, corneal exposure and drying may be followed by erosion, perforation, and infection of the anterior chamber or panophthalmitis. Other serious complications include papilledema, optic neuropathy, glaucoma, retinal detachment, and thrombosis of the retinal veins or arteries. Occasionally the tremendous increase in intraorbital pressure causes complete extrusion of the globe. The congestive and infiltrative phenomena described above tend ultimately to be followed by more permanent changes, which may appear at any stage of progression. These include induration of the lids, fibrous pseudohypertrophy of the extrinsic muscles, and fibrosis or brawny induration of the retrobulbar tissues producing irreversible proptosis. Occasionally several spontaneous partial remissions and exacerbations of the congestive and infiltrative phase may occur prior to the advent of the more permanent changes. Complete recession of proptosis is rare when the congestive and infiltrative phenomena have become well established, although a misleading impression of recession may result from a decrease in lid retraction.

The exophthalmos is often asymmetrical and may appear to be unilateral temporarily in the early stages or occasionally throughout the entire course of the disorder. This sometimes renders difficult its differentiation from orbital tumors and inflammatory pseudotumors and other nonendocrine lesions. Its tendency toward subsidence following the administration of corticotropin and adrenal steroids has been utilized [2] in differential diagnosis, but the usefulness of this procedure seems doubtful.

Sympathetic hypertonus associated with hyperthyroidism may play a minor role in causing lid retraction, and occasionally extrinsic muscle weakness may be a manifestation of widespread thyrotoxic myopathy. Such changes as the proptosis, the palprebral edema, and the chemosis can be explained by the pathological processes in the extrinsic muscles and retrobulbar orbital tissues, but the cause of the latter remains obscure. Interest in the adenohypophysis as an etiologic factor stimulated a series of investigations which strongly suggested that this gland was involved in some way in the pathogenesis of the orbital and muscular changes. Changes resembling those seen in human endocrine exophthalmos were produced by several investigators in experimental animals by the injection of various kinds of extracts of the adenohypophysis. Increased thyrotropin activity was reported in the serum of some patients with severe endocrine exophthalmos, but this has not been a consistent finding. Conflicting results have also been reported concerning the production of experimental exophthalmos with adrenal steroids. For a time it was believed that the excessive or uninhibited action of thyrotropin was responsible, but the work of Jefferies [3] and others indicates that this is not a tenable explanation. Friedgood [4] in 1941 suggested the existence of a specific ophthalmotropic principle in the adenohypophysis, and the recent work of Dobyns and his associates [5] has tended to support this concept. They have demonstrated the production of exophthalmos in the Atlantic minnow by pituitary extracts which contain none of the other known hormonal principles of this gland, and they have also produced exophthalmos in the same fish by the injection of serum from patients with hyperophthalmopathic Graves' disease.

[5] References 5 and 6.

However, even if the existence of such a specific exophthalmos-producing substance is eventually established, several important questions remain to be answered. These include the following: 1. What is the mode of action of this substance upon the retrobulbar orbital tissues and the extrinsic muscles of the eye? 2. Is its secretion controlled by hypothalmic influence, as is the case with most or all of the other known adenohypophyseal principles? 3. Is it a normal secretory product, prevented from exercising its effect under homeostatic conditions by some regulatory mechanism, or is it a pathological product released only under abnormal circumstances? 4. What factors may operate to release such normal inhibition, or to provoke the secretion of such an abnormal substance, and what role in particular may the thyroid play in such a mechanism? It is to be hoped that further exploration of these recently opened avenues of investigation will throw more light upon these and other questions and help us finally to understand this fascinating and mysterious problem, so important to ophthalmologist and endocrinologist alike.

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Treatment of Exophthalmos from the Viewpoint of an Internist

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The medical treatment of endocrine exophthalmos (malignant exophthalmos, progressive exophthalmos, metabolic exophthalmos, exophthalmic ophthalmoplegia, or hyperophthalmopathic Graves' disease) has long been more speculative than definitive, as might be expected in a condition whose etiology is not known. Each recommended method of therapy has been reported to have varying degrees of efficacy in different hands, none being beneficial in every case. Evaluation of specific therapeutic measures is difficult because the numbers of cases in reported series are usually small, the criteria used to estimate the severity of the ophthalmopathy and its degree of response to therapy lack uniformity, and therapeutic regimens vary greatly, with several methods of treatment frequently being employed simultaneously. In addition, the possibility of spontaneous remission must be considered. Until more evidence based on uniform observations is available, or until the etiology and pathological physiology of this puzzling disturbance are ascertained, no dogmatic statement regarding its proper definitive treatment can be made. Nevertheless, a brief review of the various recommended therapeutic measures in the light of the present status of knowledge in this field might be helpful.

Preliminary Considerations

Although the precise cause of endocrine exophthalmos remains a mystery, certain factors are recognized as probably playing roles in its development. These are (1) stress, especially of a nervous or emotional type; (2) pituitary dysfunction; (3) thyroid dysfunction, and (4) an increased amount of fluid in the orbital tissues.

A history of severe nervous or emotional stress preceding the onset of exophthalmos has been repeatedly encountered. Although the very nature of modern existence makes it difficult for anyone to avoid almost continuous exposure to stressful situations of one kind or another, the occurrence of a particularly distressing experience preceding the development of eye symptoms is sufficiently frequent to arouse a strong suspicion that a causal relationship exists. Means [1] considers severe ophthalmopathy to be a part of the spectrum of Graves' disease, a pathological state in which the precipitating nature of stress is perhaps more generally recognized. Why one person under suitable stress will develop ophthalmopathy; another, classical Graves' disease; another, hypertension, and another, a peptic ulcer is one of the most challenging problems in current medical research.

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The probable relationship of pituitary dysfunction to the development of ophthalmopathy has been foremost in the minds of workers in this field since Schockaert first described the production of exophthalmos in ducks following injections of pituitary extract (1931)[2]. Because clinical exophthalmos was so frequently associated with hyperthyroidism, and because pituitary extracts rich in thyrotropic hormone (TSH) were found to be particularly effective in producing exophthalmos in either intact or thyroidectomized animals, it was initially assumed that TSH was the responsible factor. Later, serious doubts were raised regarding the validity of this assumption. First, most patients with hypothyroidism, the condition in which an elevated level of TSH in the blood * and urine † has been most consistently demonstrated, do not develop exophthalmos. Second, although some patients with ophthalmopathy have been found to have elevated levels of TSH in the blood or urine, many have not.‡ Third, preparations of pituitary extract in which TSH had been inactivated still produced exophthalmos in guinea pigs,[17] and, fourth, fractionation of pituitary extracts has demonstrated that the thyrotropic and exophthalmic factors can apparently be separated.[18] Furthermore, the administration of TSH to human subjects for periods up to 22 days has failed to produce significant changes in exophthalmometer readings.[19] There is still much debate concerning the role of TSH in the production of ophthalmopathy, but it seems safe to say that at the moment the evidence is against TSH alone being a causative factor. The possibility that under suitable circumstances it may have a contributing influence has not been excluded. The nature of the primary exophthalmos-producing factor is still obscure. It may be some as yet unknown pituitary fraction, or it may result from an abnormal response of peripheral tissues to pituitary stimulation of undetermined type.

The role that thyroid dysfunction may play in the development of exophthalmos is even more uncertain. Most cases of exophthalmos are associated with clinical findings of thyroid dysfunction, and there is evidence that at least some of the apparently euthyroid cases of this condition may have laboratory findings indicative of disturbed thyroid function.§ Nevertheless, the observation that experimental exophthalmos can be produced in thyroidectomized animals is somewhat against an abnormal function of the thyroid gland per se being an essential factor. Yet, in human subjects, it might have a contributing effect.

Whatever the uncertainties concerning the roles of the first three possible factors, there is unanimous agreement that the development of exophthalmos, both clinical and experimental, is associated with an increased amount of fluid in the orbital tissues. The mechanism of deposition of this fluid has been completely obscure, but the most attractive explanation so far proposed is that it may result from an increased deposition of a mucopolysaccharide which has a strong property of binding water. Excessive amounts of such a substance have been demonstrated in the orbital tissues of exophthalmic animals.|| This mucopolysaccharide behaves in a manner that suggests that it may be hyaluronic acid, a strongly hydrophilic compound which is an important component of mucin and of the ground substance of connective tissue. In excessive quantities it might cause increased retention of fluid. Asboe-Hansen [23] has presented suggestive evidence

* References 3-9.

† References 3 and 10-14.

‡ References 8, 9, 15, and 16.

§ Reference 20 and Jefferies, W. McK.: Unpublished data.

|| References 21 and 22.

that hyaluronic acid is produced by the mast cells in connective tissue, and he and Iversen ¶ have reported that an infiltration of the retrobulbar tissues with these cells accompanies the development of experimental exophthalmos. Other studies by these workers [16] have demonstrated the deposition of abnormal quantities of this mucopolysaccharide in skeletal muscles of all of 10 patients with progressive exophthalmos and in 9 of 21 persons with hyperthyroidism, and they postulate that this may be a factor in the development of muscular weakness and ophthalmoplegias in such cases. They report that pituitary extracts rich in TSH cause an increased quantity of mast cells and hyaluronic acid in connective tissue of either intact or thyroidectomized animals, whereas either thyroxin, corticotropin (ACTH), or cortisone causes a decrease in these cells.# Cavallero and Braccini [26] also observed that cortisone caused a decrease in the number of mast cells in connective tissue of the rat. On the other hand, Devitt and his associates [27] were unable to confirm the inhibitory effect of cortisone and thyroxin on mast cells. Furthermore, Aterman [28] and Smelser and Ozanics [29] report that corticotropin and cortisone, although without ophthalmogenic activity when administered alone, have an enhancing action in the production of experimental exophthalmos by pituitary extracts. Obviously further work is necessary to reconcile these apparently conflicting observations.

Since one line of experimental work suggests that corticotropin and cortisone may counteract changes which may play a part in the development of exophthalmos, whereas the other suggests that these agents may aggravate the disturbance, one must turn to the reports of clinical trials in an attempt to find an answer to the question of their place in the therapy of this condition. The first report of the effect of these hormones in exophthalmos was a favorable one.[30] Subsequent reports were inconsistent: In some cases results were good; in others no apparent effect was noted.* In an attempt to clarify the value of these agents in this condition the British Medical Research Council conducted a cooperative study in which the observations of several clinics were pooled.[35] In a total of 28 patients with exophthalmos in various stages treated with either corticotropin or cortisone a good response was observed in 3, slight temporary improvement in 5, and no significant improvement in 20. The largest dose used was 100 mg. per day. From their data it appeared that the cases in which these agents were most likely to prove beneficial were those of relatively recent onset with congestive phenomena, such as chemosis. It was pointed out that the doses employed may have been inadequate and that larger doses should be tried. This conclusion was influenced by the report of Kinsell, Partridge, and Foreman [36] that combined therapy with larger doses of corticotropin and cortisone produced significant decrease in exophthalmos within 48 hours in nine cases of severe exophthalmos. These results were undoubtedly the most dramatic of any that have been observed in a comparable series of cases to date. Rubin and Billet,[37] employing a regimen similar to that recommended by Kinsell and his associates, obtained similar dramatic results in a single case. In none of these reports has there been any indication that these agents aggravate exophthalmos. Hence, clinical experience has been more consistent with the experimental work which suggested that corticotropin and cortisone should benefit endocrine ophthalmopathy.

¶ References 22 and 24.

References 22, 24, and 25.

* References 31-34.

If the increased fluid content of the orbital tissues in exophthalmos is due to deposition of excessive quantities of hyaluronic acid, it might be postulated that hyaluronidase, an enzyme which causes breakdown of this mucopolysaccharide, would decrease the proptosis. Nuzum [38] attempted to test this hypothesis by studying the effect of injecting hyaluronidase into the orbits of guinea pigs made exophthalmic by injections of pituitary extract. He observed a definite transient decrease in exophthalmos which lasted for a maximum of 24 hours, but the necessity of repeated orbital injections prevents this from being a practical therapeutic procedure.

Therapeutic Measures

In view of these considerations the following measures are suggested as the most rational approach to the treatment of endocrine ophthalmopathy in the light of present knowledge:

1. *General Supportive Measures.*—An attempt should be made to correct any poor living habits, with special attention to avoidance of excessive fatigue, either physical, nervous, or ocular. Diet should be well-rounded and nourishing, with supplementary vitamins. The possible relationship of nervous or emotional strain to the eye disturbance should be discussed with the patient, and an effort should be made to assist him in resolving any psychiatric problems. In some instances, the use of tranquillizing drugs may be helpful. In others, the aid of a psychiatrist may be advisable.

2. *Local Management of Eye Symptoms.*—This aspect of the therapy should be carried out by a competent ophthalmologist. It includes palliative treatment to ease ocular discomfort; protective measures to avoid eyestrain, corneal ulceration, and ophthalmitis, and corrective measures to restore maximal ocular function after the pathologic process has subsided. Close cooperation between the internist and ophthalmologist is of great importance in the management of these cases.

3. *Treatment of Thyroid Dysfunction if Present.*—Although there is much disagreement regarding the details of management of this aspect of the disturbance, it would seem reasonable first to test carefully for the presence of thyroid dysfunction, even in those cases which appear to be euthyroid, utilizing methods such as radioactive iodine uptake, serum protein-bound iodine, and butanol-extractable iodine, and then to try to correct any abnormality found. If hypothyroidism is present, desiccated thyroid should be administered. This medication has also been recommended for cases of exophthalmos with euthyroidism on the basis of its theoretical inhibitory action on the pituitary or its effect on mast cells, but its effects on the eye disturbance are usually not dramatic. If hyperthyroidism is found, potassium iodide is usually adequate to control milder cases. In some instances its administration is followed by development of symptoms or signs of hypothyroidism, and in such patients the addition of desiccated thyroid appears to be beneficial. In other cases symptoms suggestive of hyperthyroidism, such as increased nervousness and tension, may be associated with other features more consistent with hypothyroidism, such as slow pulse and sensitivity to cold. Here combined therapy with potassium iodide and desiccated thyroid is usually helpful. For the management of severer degrees of hyperthyroidism radioactive iodine appears to be preferable to subtotal thyroidectomy, since it involves less acute stress, but severe ophthalmopathy has occurred after therapeutic radioactive iodine as well as after surgery, and patients so treated must be followed carefully. In general it appears that thiouracil derivatives should be used with caution if at all in cases

with endocrine exophthalmos. Their action enhances pituitary activity, and several instances of aggravation of ophthalmopathy during their administration have occurred.

4. *Corticotropin and Hydrocortisone or Related Steroids.*—In view of the reports of dramatic effects following administration of large doses of these agents, further trials at high dosage levels, particularly in cases of recent onset with acute congestive phenomena, appear warranted. An initial dosage of 40 units of corticotropin in 1000 ml. of 5% dextrose solution intravenously over a 10-hour period plus 200 mg. of hydrocortisone by mouth for the first two days should be tried, with subsequent decrease in dosage according to individual conditions. In order to lessen the danger of the undesirable side-effects of hypercorticism, a low-sodium diet with added potassium chloride should always accompany this therapy, and concurrent testosterone administration may help to counteract the negative nitrogen balance. The use of prednisone or prednisolone in a dosage of 40 mg. daily instead of hydrocortisone should avoid the hazard of sodium retention, but gastrointestinal symptoms are commoner with these two agents. Aluminum hydroxide gel may be given in an attempt to avoid this complication.

5. *Irradiation.*—The effects of irradiation of the pituitary or orbits upon exophthalmos have varied in different clinics,† but a sufficient number of favorable results have occurred to make this therapy worthy of consideration in patients who fail to respond to more conservative measures. A dosage of at least 3000 r delivered to the pituitary seems advisable, and the chances of improvement appear to be greater in cases of less than one year's duration.

6. *Orbital Decompression.*—In severe progressive cases in which vision is acutely threatened and which do not respond within 72 hours to intensive therapy with corticotropin and hydrocortisone, surgical decompression of one or both orbits may be necessary. In capable hands the results may be dramatically beneficial.‡

Summary

A brief review of the therapeutic measures which have been recommended for cases of endocrine exophthalmos is presented, with emphasis on the medical aspects in the light of the current status of knowledge of this puzzling disturbance. As a general principle, it is felt that milder cases can usually be managed by conservative methods, whereas acute, fulminating cases warrant more vigorous therapy, such as large doses of corticotropin and hydrocortisone or related adrenal steroids or surgical decompression. Until the etiology and pathological physiology of this condition are known, no dogmatic statement can be made regarding its definitive treatment. In the meantime, evaluation of different methods of therapy would be easier if all reports would include specific measurements of the pertinent aspects of ophthalmopathy, such as exophthalmometer readings and perimeter charts, as well as careful estimates of the degree of chemosis and periorbital puffiness, before and during the course of treatment.

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Treatment of Exophthalmos from the Ophthalmologist's Viewpoint

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As I collected material for this symposium, I wondered how many conditions might produce exophthalmos, for treatment can be chosen more rationally if a definite cause for ocular protrusion can be established. I consulted the oracle, Sir Stewart Duke-Elder, and found that more than 70 distinct entities were listed in his textbooks of ophthalmology as capable of producing exophthalmos. Obviously, one cannot go through the mental calisthenics necessary to make a differential diagnosis among such a large number of disorders every time a patient who has exophthalmos walks into the office.

To simplify diagnosis and the approach to therapy, I consider only four general categories when I am confronted with exophthalmos. I ask myself four questions: "Is it inflammatory?" "Might it be a vascular anomaly?" "Could it be metabolic exophthalmos?" "What about the possibility of tumor?" Once the case is catalogued into one of these four groups, the problem of treatment is then considered.

With regard to therapy, most of the statements in this paper will be applicable to unilateral or asymmetric exophthalmos rather than to bilateral exophthalmos, for the former conditions offer more of a challenge to diagnosis and treatment. The question of exophthalmos in children will be excluded from this discussion. The words "exophthalmos" and "proptosis" will be used in the sense that they are rather interchangeable in meaning.

Inflammation

Inflammatory lesions in the orbit that produce exophthalmos often originate in structures adjacent to the orbit and spread to the orbit by reason of the many fissures and foramina in the orbital walls and because of the free venous interchange between the orbit and adjacent structures. Less often, the inflammation is primary in the orbit or reaches the orbit by metastatic spread.

All the inflammatory disorders that affect the orbit have the pattern of symptoms that are common to inflammation as it occurs anywhere in the body. Pain, heat, swelling, and tenderness of the orbital structures are encountered oftener in association with the early stages of inflammatory exophthalmos than they are in any of the other three main categories of exophthalmos.

When the ophthalmologist is confronted with exophthalmos in which an inflammatory origin appears probable, further differential diagnosis is considered.

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I ask myself if the clinical clues point to involvement of any particular structure within the orbit, such as the lacrimal gland, bone, blood vessels, fascia, or muscle. The conditions that produce the majority of the inflammatory changes within the orbit are listed in Table 1.

TABLE 1.—*Common Inflammatory Conditions of the Orbit That Produce Exophthalmos*

Orbital cellulitis secondary to sinusitis
Intermittent edema of unknown origin (allergic?; vasomotor?)
Collagen disorders
Thrombophlebitis
Dacryoadenitis
Tenonitis
Osteomyelitis and periostitis

The management of these inflammatory conditions generally is nonsurgical, at least from the standpoint of the ophthalmologist. When orbital cellulitis is secondary to sinusitis, the otorhinologist may wish to eradicate the primary infection by surgical means, but the ophthalmologist is wise to avoid surgical maneuvers in such orbits.

It is in this group of inflammatory lesions that the ophthalmologist most often employs antibiotics, steroid hormones, antihistaminics, and nonspecific foreign protein. Although inflammatory lesions were the commonest cause of exophthalmos 20 or 30 years ago, this group appears to have become less and less of a factor in the production of proptosis with the passage of time.

Vascular Anomalies

This second main group of orbital conditions producing exophthalmos includes the orbital varix and arteriovenous aneurysms and fistulas. These vascular disorders can be discussed as a group, for their symptoms, clinical course, and treatment differ considerably from those of the other orbital diseases associated with proptosis. The proptosis in such cases may be transient, intermittent, or pulsatile, in contrast to the more steadily progressive exophthalmos of other dis-

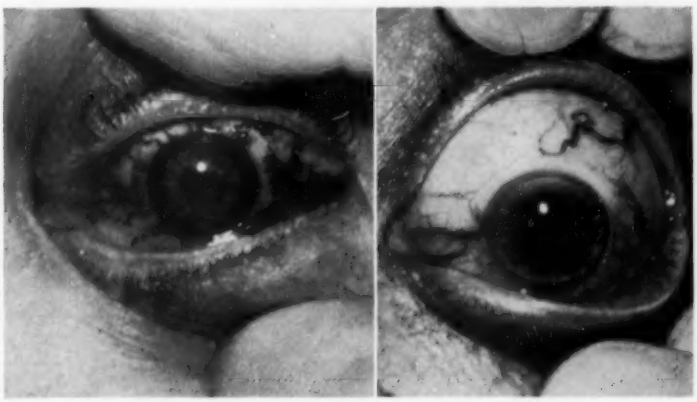

Fig. 1.—Two examples of dilatation of the veins on the surface of the eyeball as the result of vascular disturbances within the orbit.

eases. Engorgement of the veins in the orbit and on the surface of the globe will develop at some phase of their clinical course (Fig. 1). The retinal veins often are dilated and full. The intraocular pressure also may be increased on the side of the lesion. A bruit or thrill may be demonstrated.

When persistence of the proptosis makes it necessary to treat the lesion, there is little choice other than a surgical approach. These vascular anomalies are one of the most difficult situations that confront the orbital surgeon because of the chance of encountering a nest of uncontrolled bleeders and because it is so difficult to root out the many ramifications of these lesions in the deeper portions of the orbit. Also, the patients frequently are disappointed in the results of surgical intervention because of incomplete removal or recurrence of the vascular lesion. Even when good surgical resection has been obtained, the proptosis may not subside to the satisfaction of the patient because the tissues have been stretched beyond the point of reversible elasticity by reason of the long duration of the lesion within the orbit.

Arteriography with the aid of a contrast medium injected into one of the carotid arteries has been of help in determining the extent of the vascular involvement and how best to approach it. The help of the neurosurgeon always should be obtained for this procedure. If the angiogram shows involvement of some of the intracranial vessels, further care of the patient should be under the jurisdiction of the neurosurgeon, but if the vascular involvement appears to be confined to the orbit, then treatment becomes the responsibility of the ophthalmologist.

The main goal of the surgical approach is to get beyond the region of the dilated vessels and shut off the feeder channels. It is often extremely difficult to accomplish this when the lesion lies deep in the orbit. Most vascular anomalies occur in the upper quadrants of the orbit. If the lesion appears to lie in the upper nasal quadrant, I approach it through an incision in the brow, first ligating the facial artery and vein near the inner canthus. If the anomaly involves the upper outer quadrant, I approach it through the lateral route (modified Krönlein operation).

To eradicate these anomalies, I use a combination of excision, ligature, and electrocoagulation. After excising as much as possible of the mass and electrocoagulating or strangling whatever remains, I usually leave a few radon seeds in the operative site before closing the incision.

Metabolic Exophthalmos

Metabolic exophthalmos refers to a tissue change that occurs in both orbits due to some upset in the thyroid-pituitary relationship which results in protrusion of the eyes. This form of exophthalmos may be associated with hyperthyroid, hypothyroid, or euthyroid states. It is always bilateral but often is so asymmetric that it may be considered mistakenly to be unilateral. Table 2 lists some of the commoner terms by which this form of exophthalmos has been designated.

TABLE 2.—*Common Terms Used to Designate Metabolic Exophthalmos*

Hyperophthalmopathic Graves's disease	Exophthalmic ophthalmoplegia
Endocrine	Progressive
Thyrotropic	Malignant
Pituitary	

The medical management of the thyroid-pituitary disturbance should be left strictly to the supervision of the internist, for the ophthalmopathy is but one manifestation of a systemic disease that affects other organs and tissues. The ophthalmologist should take an active role in management when the question arises as to what might be done surgically to relieve the proptosis. In this respect, the ophthalmologist is most concerned with the so-called exposure of the eyes.

The word "exposure" apparently means different things to different ophthalmologists. In terms of surgical treatment, I think of "exposure" as being of three different types. A patient with extremely prominent eyes is shown in Figure 2*a*.

Fig. 2.—(*a*) Exophthalmos associated with pronounced retraction of the eyelids. (*b*) Results of lateral tarsorrhaphy in another patient for retraction of the eyelids. The adhesion between the eyelids is scarcely noticeable.

The word "exposure" often is applied mistakenly in this situation. The eyes in this case looked exposed because of pronounced retraction of the eyelids. However, the actual measurements as determined by use of the Hertel exophthalmometer were only a little above the normal range. The retraction of the eyelids as measured by the width of the palpebral apertures was 18 mm., a measurement nearly twice the normal average. In spite of the great retraction of the eyelids, this patient still could close the eyes, and the corneas were covered adequately even during sleep. Such proptosis is not an example of true exposure, because keratitis will not develop simply because the eyes are prominent. The ophthalmic surgeon need not be hurried into doing something surgically in this situation, because the condition is not so bad as it appears.

However, patients who have such extreme prominence of the eyes often complain a great deal about the ocular irritation and tearing that result from superficial drying of the cornea. If the situation becomes too annoying, such as in farmers and millworkers who are exposed to a great deal of dust, or if the patient is a woman who is greatly upset by reason of her appearance, lateral tarsorrhaphy is recommended. Tarsorrhaphy refers to actual surgical union between the tarsal plates. This operation is chosen because the resultant union will not stretch as much as will intermarginal adhesion of the eyelids of the same width. In women, tarsorrhaphy adds a great deal to the cosmetic appearance by permitting more coverage of the globe by the eyelids and diminishing the appearance of stare (Fig. 2*b*).

Another type of "exposure" is illustrated in Figure 3*a*. At first glance this

Fig. 3.—(*a*) Because of severe ophthalmoplegia, the eyeball cannot be rotated upward. The integrity of the cornea is endangered by desiccation. (*b*) Protrusion of conjunctiva in the interpalpebral zone near the inner canthus because of chemosis.

situation may look quite similar to the first type in that prominence of the eye and retraction of the eyelids are present. However, the patient pictured in Figure 3*a* had complete paralysis of upward gaze as the result of severe ophthalmoplegia, and the eyeball would not roll up beneath the lid when the patient was asleep. This patient presented an instance of true exposure, for the cornea was in imminent danger of breakdown due to desiccation. For this situation, I favor the performance of two-point intermarginal adhesion of the eyelid. The portions of the eyelids chosen for intermarginal adhesion roughly correspond to the nasal limbus and temporal limbus of the eyeball. Such adhesion will permit a central peephole for the patient, thus keeping him ambulatory, and yet provide sufficient coverage of the cornea to prevent keratopathy. Although some stretching of such adhesions might occur, I have not found this to be a problem because the proximity of the adhesions tends to nullify this factor.

The third type of "exposure" is illustrated in Figure 3*b*; in addition to proptosis, retraction of the eyelids, and some ophthalmoplegia, congestion of the eyeball and chemosis are present. In this situation, the cornea does not necessarily break down because of desiccation but apparently undergoes a nutritional disturbance because the edematous conjunctiva forms a collarette of pressure around the limbus and interferes with the metabolic interchange. Decompression of the orbit is recommended for this situation.

For some years I considered that the transfrontal route offered the best approach to orbital decompression, but more recently, because of certain improvements in technique, I think that the lateral approach (modified Krönlein operation) is the best solution to the problem. The Stryker oscillating bone saw and use of a simple horizontal incision posterior to the lateral canthus are the two major improvements in surgical technique that have made the lateral approach more widely used. The incision need not be longer than 4 cm., and it is not necessary to incise the lateral canthus (Fig. 4*a*). The site of exposure in the lateral orbital wall created by this approach measures about 3 cm. in diameter (Fig. 4*b*). Another advantage of the lateral over the transfrontal route is that patients appear to accept the former technique with fewer misgivings. Many

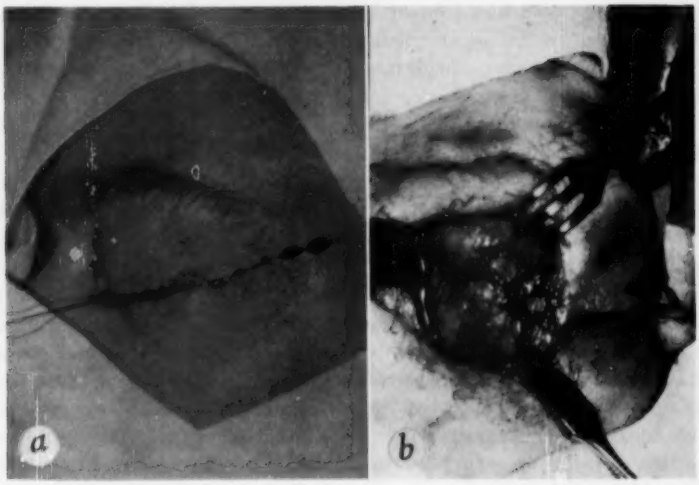

Fig. 4.—Orbital decompression by the lateral approach. (*a*) Recommended incision; the lateral canthus need not be included in the incision. (*b*) Exposure of the orbital contents through the lateral approach. The bone flap is hinged to the temporalis muscle and is retracted posteriorly beneath the large retractor.

patients are naturally reluctant to submit to an intracranial procedure if another route can be chosen. Women in particular are likely to resist the transfrontal approach because of their fear of a disfiguring scar. Thus, use of the lateral approach often permits the surgeon to operate earlier than would otherwise be possible, and rather general agreement exists among neurosurgeons and ophthalmologists that the benefits from orbital decompression are often proportionate to how early in the course of the disease the operation is performed.

Orbital Tumors

In this fourth category, tumor is used in its broadest sense to indicate any mass, other than the ones already considered, that produces proptosis. Used in this manner, the term includes, in addition to neoplasms, a condition that appears at present to be rather frequently recognized and recorded in the literature, the so-called pseudotumor. From the pathologist's standpoint, a pseudotumor is an inflammatory lesion. When the pseudotumor is in the anterior portion of the orbit, it sometimes produces sufficient swelling and redness of the eyelids to allow a presumptive diagnosis of this condition. In the majority of cases, however, a pseudotumor cannot be absolutely distinguished from a neoplasm until the surgeon has uncovered the mass. In their initial stages of growth, pseudotumor and true neoplasms produce such a similar pattern of symptoms that it is practical to group them together as a separate category producing proptosis.

The most characteristic symptom of orbital tumor is displacement of the globe in one direction or another without significant edema of the eyelid or appreciable alteration in the width of the palpebral aperture in the early stages; it is associated with minimal ophthalmoplegia and congestion of the eyeball as compared with the categories discussed previously. The exception to this rule is the tumor located within the muscle cone. Here, however, loss of vision usually precedes the proptosis.

The treatment of orbital tumors is primarily surgical. If the mass can be

palpated by digital pressure, I favor an anterior approach, using a brow incision for tumors located in the upper quadrants and an incision along the lower orbital rim for lesions in the lower quadrants. If the mass cannot be palpated and pronounced loss of vision has not occurred, I approach the tumor through the lateral wall. If the mass cannot be palpated and severe loss of vision is present, the transfrontal approach is recommended.

The surgeon always should approach surgical inspection of the orbital tumor as though the worst might be found. Prior to operation, the surgeon should ask the patient's permission to remove the eye should a malignant lesion be found that cannot be removed successfully without enucleation. As the orbitotomy commences, my goal is to find out what type of lesion is in the orbit and remove the lesion if necessary. I do not believe in so-called exploratory orbitotomy or needle biopsy. I do not approve of opening an orbit simply to find out what is there, taking a sample of tissue for pathologic study, closing the orbit, and then waiting a few days to decide what specific measures should be undertaken.

If an encapsulated mass is found, it is removed entirely and sent for pathologic study. If the mass is not encapsulated, a representative section of the tumor is removed and the report of pathologic study on the frozen tissue is awaited before anything further is done. If the tissue proves to be pseudotumor, I take out as much of the mass as can be removed conveniently without harm to surrounding structures, close the incision and give supplementary x-ray therapy. If the lesion is a benign nonencapsulated neoplasm, I also remove as much of the tumor as possible and decide the question of supplementary x-ray therapy on the basis of the apparent radiosensitivity of the tissue. If the tissue proves to be a malignant lesion of the radiosensitive type, I likewise remove as much of the tumor as possible and treat the remainder with x-rays. If the report indicates a malignant tumor of the radioresistant type, I complete the operation by total removal of the mass and whatever orbital structures are attached to it. Thus, the majority of orbital tumors can be handled by one operation.

Summary

The many conditions within the orbit that may produce exophthalmos can be considered from the standpoint of four main categories, namely, inflammatory lesions, vascular anomalies, metabolic disturbances, and orbital tumors, including pseudotumor.

The management of inflammatory lesions is generally nonsurgical. Eradication of vascular anomalies is best done by a combination of excision, ligature, and electrocoagulation. The medical management of metabolic disturbances leading to exophthalmos should be left to the internist, with the ophthalmologist taking over when surgical relief of the proptosis is considered. The treatment of orbital tumors is primarily surgical, often supplemented by x-ray therapy.

The Relation of Horizontal Saccadic and Vergence Movements

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and
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When an observer with normal eyes is instructed to shift his gaze suddenly from one fixated point in the visual field to a second, the time characteristics of the movements of the eyes depend upon the positions of the two points within the field. Dodge [1] pointed out that if the two points are confined to the horizontal plane which includes the centers of rotation of the two eyes then two basic types of movements can be differentiated according to the velocity of the movement:

(*a*) If the two points are confined approximately to an objective fronto-

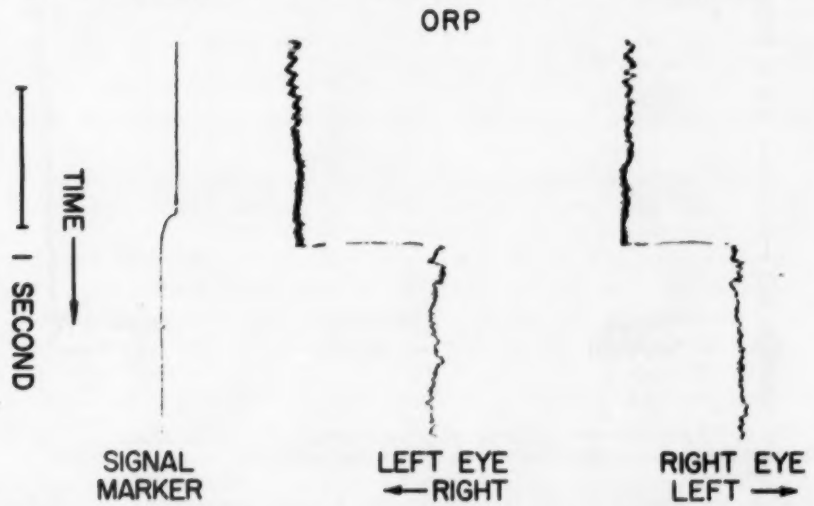

Fig. 1.—Ocular rotational potential of saccadic movement (a term suggested by Prof. H. R. Blackwell). The observer was fixating a light in the straightforward position. At the signal mark the fixated light was turned off and a second light in the same plane as the first but 8 degrees to its left was turned on. The movements of the two eyes have been recorded by placing electrodes on both canthi of each eye and amplifying the resulting difference in potential, as described by Marg.[17] (These records were obtained with the assistance of Dr. O. T. Law Jr. and Dr. R. L. De Valois).

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parallel plane, then the movement is very rapid (Fig. 1). The velocity of this movement may be higher than 400 degrees per second and increases as the separation of the fixated points increases. Such movements are called saccadic movements. A detailed analysis of some of their characteristics has been recently made by Westheimer.[2]

(*b*) If the points are so arranged that they fall on a forward extension of the median body plane, then the movement is much slower (Fig. 2). For our

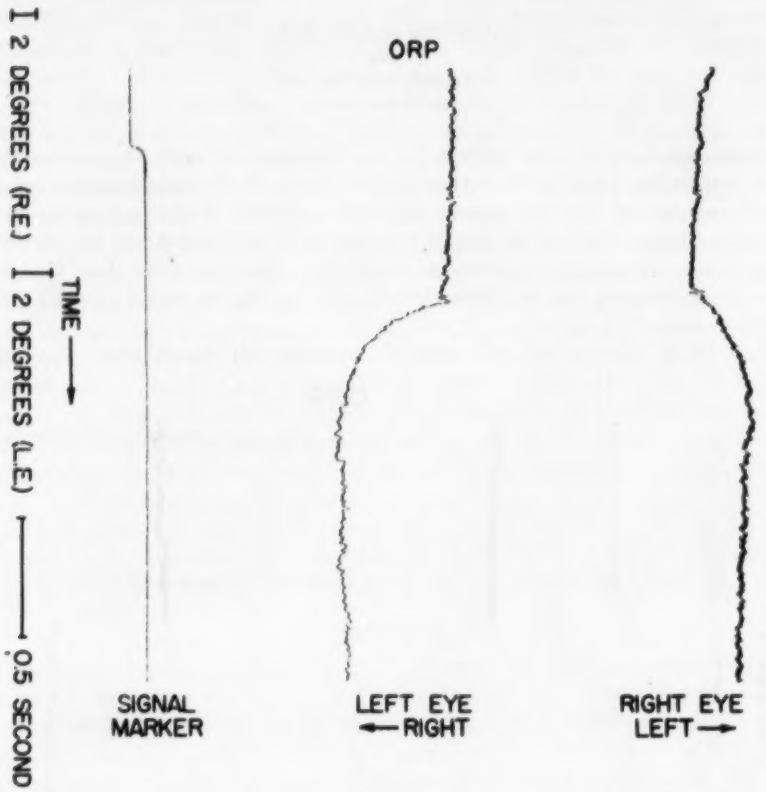

Fig. 2.—Ocular rotational potential of a symmetrical convergence movement. The far and near targets are vertical plumb lines on a white background.

observer the average velocity is approximately 8 degrees per second, and Dodge [1] reported values ranging from 25 degrees per second to 10 degrees per second. Such movements are called vergence movements.

Dodge also pointed out that if the points (still in the horizontal plane) are intermediate between these two positions then the change of fixation of the eyes from the one point to the second will contain both of the basic types of movements. Thus, if the near object is shifted so that it falls along the line of sight of the right eye (while it fixates the far object) then the result of binocular shift from far to near contains a saccadic fast component to the right and a slow component of convergence (Fig. 3). It is interesting to point out that for this observer both eyes move. This confirms Dodge's results completely,

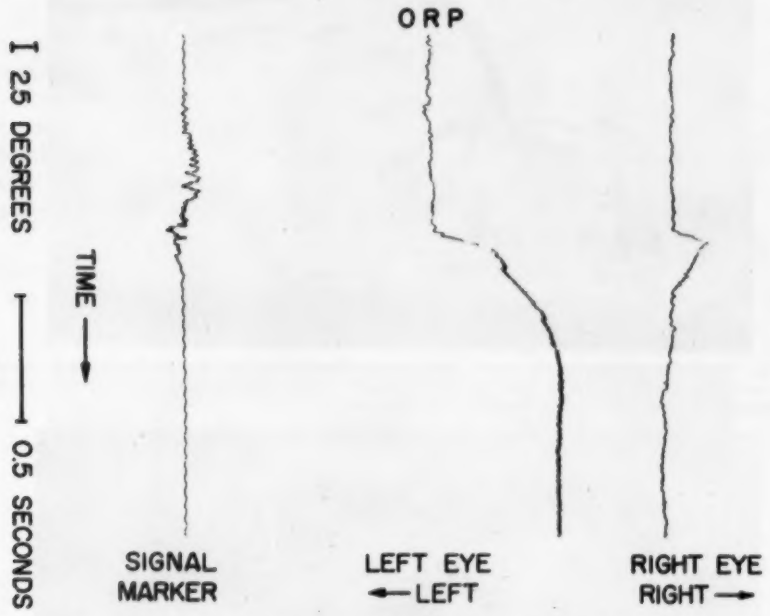

Fig. 3.—Binocular refixation from a far (3.4 meter) to a near (0.186 meter) vertical black line on a white background. The near vertical line was carefully aligned on the line of sight of the right eye while it fixated the far vertical line monocularly.

although such findings have been denied by Bielschowsky,[3] Scobee,[4] and, recently, by Breinin.[5]

What is the explanation for the difference in velocity of these two types of movements? Dodge explained it "that in all convergence movements of the eyes, each eye is retarded more or less by the tendency to move sympathetically in the same direction with the other eye." In terms of present understanding of movement patterns as described by Hartson[6] and Stetson,[7] this suggestion is tantamount to saying that convergence movements are slow tension movements in which agonist and antagonist muscles cocontract. Saccadic movements, on the other hand, if not being completely ballistic,[2] are presumably at least ballistiform, as has recently been demonstrated by Bjork,[8] using physiological techniques.*

A hint as to another possible explanation for the difference in velocity of these two kinds of movements is provided by morphological examination of those extraocular muscles which move the human eye.

The histological study of these muscles reveals an innervation which differs substantially from that of the other skeletal muscles, including the levator palpebrae. The fibers of these eye muscles are supplied by two different types of nerve fibers, both of which are apparently efferent†:

(*a*) Coarse, medullated nerve fibers form typical motor end-plates (Fig. 4) which innervate the large muscle fibers only.

(*b*) Small, nonmedullated nerve fibers form either loop-like endings close

* These same experiments demonstrate that pursuit movements of the eyes are probably of the type which Stetson described as slow tension movements.

† References 9-14.

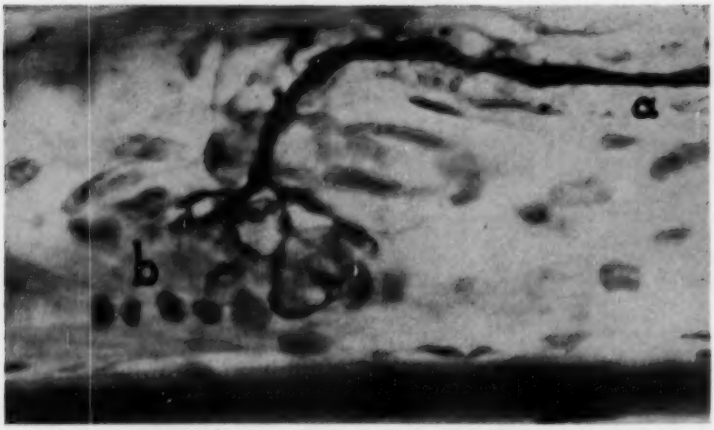

Fig. 4.—Motor end-plate (*b*) on a large striated muscle fiber of the human eye muscle (m. rect. sup.). The muscle fiber is not in focus. (*a*) Coarse, medullated nerve. Silver carbonate technique of del Rio Hortega; × 800.

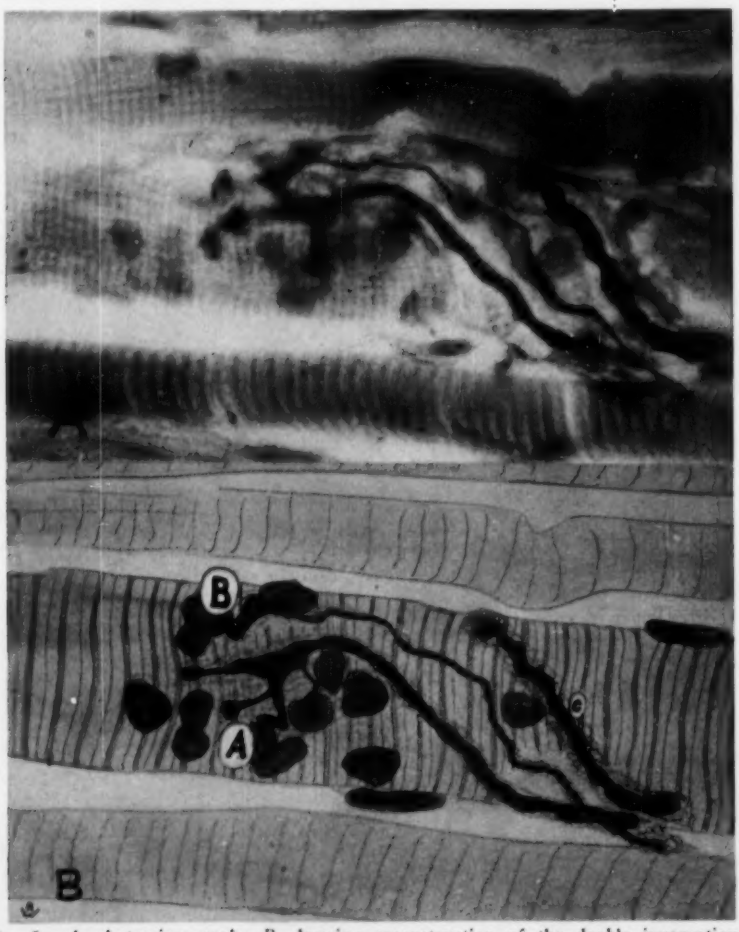

Fig. 5.—*A*, photomicrograph; *B*, drawing reconstruction of the double innervation of a large striated muscle fiber of the human eye muscle (m. rect. sup.). *A*, motor end-plate of coarse medullated nerve; *B*, simple, loop-like ending of delicate nonmedullated nerve on the same muscle fiber; *C*, another nerve fiber which is not related to the end-organ here described. Silver carbonate technique of del Rio Hortega; × 800.

to the motor end-plates or delicate network-like endings on the muscle fibers. These nerves may innervate either large muscle fibers (Fig. 5) or the small specific muscle fibers described by Woollard [15] and by Wolter (Fig. 6).‡

Boeke [9] first described this double motor innervation of the eye muscles and identified the small fibers with the autonomic nervous system. His results and conclusions have been verified completely by Kirsche [10] and by one of us.§ Wolter also showed that the human eye muscles have six distinctly different types of sensory (presumably proprioceptive) end-organs.

It seems to us that these morphological and physiological data present an interesting parallel. If this is true, then another explanation for the difference in the velocity characteristics of saccadic and vergence movements is suggested.

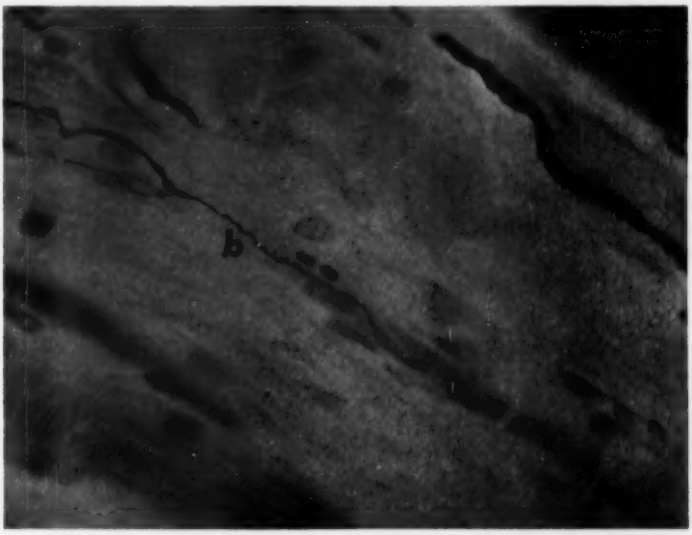

Fig. 6.—Small striated muscle fiber (*a*) with ending of a delicate nonmedullated nerve (*b*). Gros-Schultze technique; × 800.

This is that the final common paths for saccadic movements are formed by the thick somatic nerve fibers, while the final common paths for vergence movements are formed by the thin autonomic nerve fibers. There are several attractive features to such a hypothesis. In the first place, it would explain the very close similarity in the velocity characteristics of vergence movements and those of the autonomically innervated intraocular muscles.[16] It would also account for the fact that both a vergence movement and a saccadic movement can occur during a single change in fixation (Fig. 3). Thirdly, it would explain the fact that several months of experiments in vergence movements have failed to show any appreciable change in velocity characteristics in our observer. It is generally recognized that slow tension movements will become ballistiform with practice.

Finally, this speculation provides a basis for the understanding of the ability of an eye muscle to carry out a yoked movement together with a muscle of the

‡ References 11 and 12.

§ References 11-14.

other eye at one moment and at another moment during the same change of fixation carry out a second yoked movement with the latter muscle's antagonist.

The differences in these speculations and those of Dodge are very real ones which are subject to empirical test. Experiments along this line are currently in progress in our laboratories.

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The Circle of Least Confusion on Sturm's Conoid of Astigmatism

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Fortunately for most people who wear glasses, it is not essential that the examining practitioner understand all of the optical details involved before writing down the final prescription. After a reasonable amount of experience, the average refractionist finds that the technique of retinoscopy becomes almost a matter of habit, and the basic concepts underlying his procedures may soon be forgotten. Indeed, the advisability of teaching more than the descriptive aspect of optics to future oculists has recently been debated.[1] Nevertheless, it is generally agreed that a certain minimum of familiarity with the fundamental mathematical relationships is to be recommended, at least for the beginning student of refraction.

The geometrical properties associated with spherical lenses are universally included in courses for such students, but cylindrical lenses are often not as well described, even though a major percentage of the population has some degree of astigmatism requiring cylindrical correcting lenses. The concept of Sturm's conoid[2] in this connection is extremely valuable.

Most textbooks dealing with ophthalmic optics include a brief discussion of the conoid. Diagrams are presented to show the two focal lines, and reference is usually made to the interfocal circle[3] (or the circle of least diffusion,[4] or the circle[5] or disc[6] of least confusion).

However, the determination of the position of this circle is usually omitted. A number of authors state, incorrectly, that the circle is half-way between the two focal lines. Several texts point out that the circle is nearer to the first focal line, but do not give an exact indication of where. Other books contain the correct relationship,* without explanation. An algebraic derivation has been given by Eggers,[9] and there is a direct proof based upon properties of harmonic division in projective geometry,[10] but these are, in general, not suitable for the average student of refraction.

When this question arose in the optics course of the Graduate School of Medicine of the University of Pennsylvania, it was decided to attempt a simple presentation containing nothing beyond the most elementary mathematics. The following development resulted.

Location

Let us assume an ideal convex spherocylinder, with incident rays parallel to

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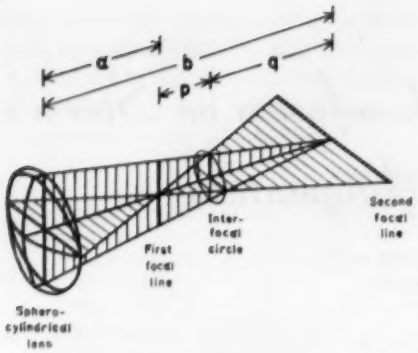

Fig. 1.—Sturm's conoid of astigmatism, showing the two focal lines, the interfocal circle, and the semiaxes of a number of elliptical cross sections.

the principal axis (Fig. 1). Let a designate the shorter of the two focal lengths, b the longer, and c the radius of the lens (or of the aperture, assumed to be circular). Let p and q signify the unknown distances from the focal lines to the interfocal circle, and r the radius of this circle.

As is often the case, it will simplify the students' understanding if the more important components are drawn separately† (Fig. 2). The essential triangles

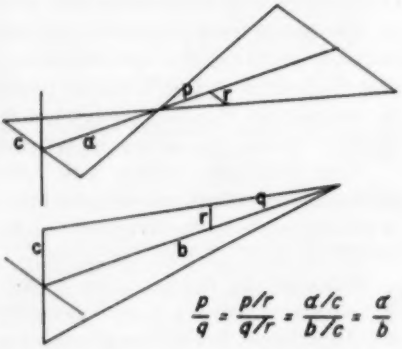

Fig. 2.—Horizontal and vertical sections of the conoid, showing the similar triangles related to radii of the interfocal circle.

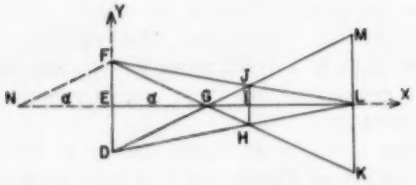

Fig. 3.—Combination of essential triangles in a single diagram, without perspective.

may then be combined in the same plane, without the perspective effect (Fig. 3). This diagram may also be looked upon as a coordinate chart, with origin at E. The X-axis may be taken to represent the distance from the lens, measured along the principal axis, of any cross section of the conoid, and the Y-direction to designate the semiaxes of that cross section. Thus, the line FL will represent the graph of the decrease in the vertical semiaxis as one proceeds away from the lens out toward the second focal line, and the broken line FGM, the corresponding horizontal dimension.

† Reference 11, p. 19.

The principal axis LE is projected backward by a length equal to the shorter focal distance, a, to the point N, and the line NF is drawn. A few basic principles dating back to the plane geometry of Euclid are now utilized‡: If two straight lines intersect, the angles opposite to each other are equal; if two triangles have two angles of the one equal to two angles of the other, the triangles are similar, and, if two triangles are similar, then corresponding lengths of the two triangles will be in direct proportion.

Since the triangles NEF and GED are congruent, the angle ENF is equal to the angle EGD, and this in turn is equal to the opposite angle LGM. We may now consider the two triangles GJL and NFL (Fig. 4). The angles at G and at

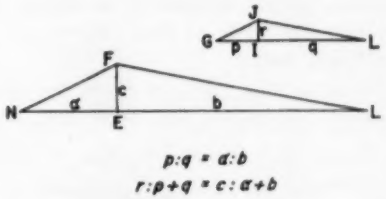

Fig. 4.—The similar triangles for a direct geometric proof.

N have been shown to be equal, and the angle at L is common to both triangles. Therefore, the triangles are similar, and any corresponding lengths will be in proportion. In particular, this may be applied to the segments into which the base of each triangle is divided by the altitude IJ or EF, respectively. It is thus seen that GI is to IL as NE is to EL, or p is to q as a is to b. This is equivalent to the statement that the interfocal circle divides the astigmatic interval of Sturm into two parts which are proportional to the two focal lengths of the dioptric system. The circle will always be located closer to the first focal line than the second, or, between the midpoint of the astigmatic segment and the first focal line.

Another straightforward derivation avoids adding lines to the diagram but depends instead upon an algebraic device. The numerator and denominator of an ordinary fraction may both be divided (or multiplied) by the same quantity without altering the value of the fraction. Making use of two pairs of similar triangles (Fig. 2), we may therefore write

$$\frac{p}{q}=\frac{p/r}{q/r} \qquad \frac{a/c}{b/c}=\frac{a}{b}$$

or

$$\frac{p}{q}=\frac{a}{b}$$

Radius

The radius of the interfocal circle, should this be desired, may be readily obtained by applying the proportionality relationship to the bases and the altitudes of triangles GJL and NFL, respectively (Fig. 4). Thus,

$$IJ:GL = EF:NL$$

or

$$r/(p+q)=c/(a+b)$$

‡Reference 11, based, respectively, upon Book I, Proposition 15 (p. 37); Book I, Proposition 32 (p. 65), and Book VI, Proposition 4 (p. 334).

Solving this equation for r, and noting that (Fig. 3) $p+q=GL=EL-EG=b-a$ we have

$$r=c(p+q)/(a+b)$$

or

$$r=c(b-a)/(a+b)$$

Having the radius, we may write the area of the interfocal circle

$$A_{circle}=\pi r^2=\pi c^2(b-a)^2/(a+b)^2.$$

Comparative Areas

There seems to be a common misconception that the area of the circle of least diffusion is less than the area of any other cross section (elliptical) of Sturm's conoid taken between the two focal lines. In order to investigate this, a minimum of information about the area of an ellipse is required. The statement by Archimedes, that the areas of two ellipses are to each other as the product of their axes,[12] will suffice.

Let us consider a cross section taken at P on the interfocal interval (Figs. 1 and 5) at a distance of s from the first focal line, t from the second focal

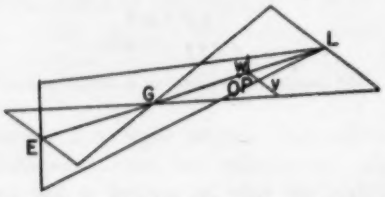

Fig. 5.—Outline of the conoid of astigmatism, showing the semiaxes of an arbitrary elliptical cross section between the two focal lines.

line, and u from the midpoint O of the interfocal segment GL. Let v represent the horizontal semiaxis of the ellipse, and w the vertical semiaxis. From similar triangles (Fig. 6), it is seen that

$$v:s=c:a$$

and

$$w:t=c:b$$

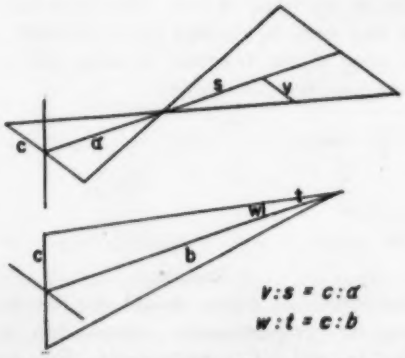

Fig. 6.—Horizontal and vertical sections, showing the similar triangles for determining semiaxes v and w.

Solving these equations for v and w and multiplying, we have

$$v=s\cdot c/a$$

$$w=t\cdot c/$$

$$vw=st\cdot c^2/ab$$

Thus it is seen that the product vw is equal to a constant c^2/ab times the product st. The sum $s + t$ is always equal to the length of the interfocal interval, and it therefore remains constant. We may now employ the algebraic result that the product of two quantities whose sum is held constant will attain its maximum value when the two quantities are equal. This statement can be proved to the satisfaction of even the most nonmathematical students as follows.

Let h represent the distance GO or OL, one-half the length of Sturm's interval. Then

$$s=GP=GO+OP=h+u$$

and

$$t=PL=OL-OP=h-u$$

Multiplying,

$$st=(h+u)(h-u)$$

or

$$st = h^2 - u^2$$

Thus, the product st is equal to the variable quantity u^2 subtracted from the fixed quantity h^2, and therefore the maximum value will be obtained when u is zero. This implies that $s=h$ and $t=h$, or that the maximum cross section area will be located at the midpoint of the astigmatic interval. Here v and w will be unequal (since $v=hc/a$ and $w=hc/b$, and a and b are unequal); consequently, the cross section will be an ellipse.

It can be seen that the larger the numerical value of u the smaller the product st, and hence the smaller the cross section area. As the value of u is increased toward h, the ellipse moves toward either G or L, and the area decreases toward the limiting value of zero. One may also state, since u appears only in the squared form u^2, that cross sections taken at equal distances in front of and behind the midpoint of the interval (u positive and negative, respectively) will have equal areas.

By examination of a graph of cross section areas plotted in terms of the position along Sturm's interval where the section is taken (Fig. 7), the following

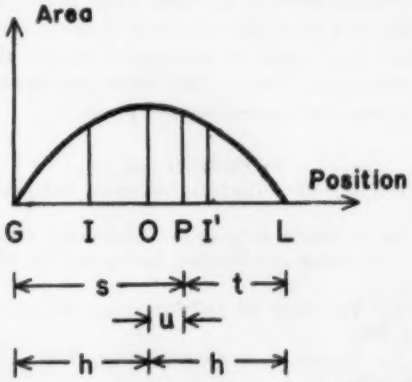

Fig. 7.—Graph of cross section area charted against location of the cross section along the interfocal interval.

will become apparent. As one moves from the first focal line toward the second, the ellipses gradually increase in area until the ellipse becomes a circle, at I. The elliptical shape is resumed beyond I, and the areas continue to increase until the midpoint O of the interval is reached. Then the ellipses decrease in

area, becoming gradually deformed into a straight segment at the second focal line. At some point on the interval, there is an ellipse with an area exactly equal to that of the interfocal circle. (This occurs at point I', which is as far beyond O as I is in front of O.)

Should one require the actual area of the maximum ellipse, the formula[13] Area $= \pi vw$ may be applied, substituting for v and w the values found previously and replacing h by $\frac{1}{2}(b-a)$.

$$A_{max} = \pi vw$$
$$= \pi h^3c^3/ab$$
$$= \pi (b-a)^3c^3/4ab.$$

This formula, as well as that for the area of the interfocal circle, contains the factors $(b-a)^2$ and c^2. These areas may therefore be reduced, and the astigmatic diffusion consequently decreased, either by minimizing the difference $b-a$ (as is done in the various refraction techniques), or by making c, the pupillary diameter, smaller.

Other Applications

In the case of an object at a finite distance in front of the spherocylindrical lens, rather than that of parallel incident rays, all of the preceding algebraic and geometric considerations will apply, with the exception that the two focal distances will no longer be the principal focal lengths. The quantitative relationships may be determined readily by means of an optics nomogram published recently.[14] Most of the discussion will also be valid for the astigmatism associated with obliquely incident rays upon a spherical lens.

Summary

It is commonly believed that the cross section of Sturm's conoid midway between the two focal lines represents the "circle of least diffusion" and that its area is less than that of any other cross section along the astigmatic interval. Actually, this cross section is always an ellipse, with an area greater than that of any other cross section between the two focal lines. The interfocal circle is located nearer to the first focal line, dividing Sturm's interval into two parts proportional to the two focal lengths of the optical system, and its area is neither a maximum nor a minimum. Proofs for these statements requiring nothing beyond elementary algebra and geometry are given.

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Unusual Myogenic Tumors Around the Eye

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I. Granular-Cell Myoblastoma

Granular-cell myoblastoma is an uncommon lesion which occurs most frequently in the tongue but has also been found in the subcutaneous tissue of the trunk and the extremities. It has been observed in the lips, the floor of the mouth, and the vocal cord. Its occurrence around the eye is so extremely rare that many ophthalmologists are not familiar with the clinical course or the histologic picture of this tumor.

The tumor has been found in the orbit [1] and in the area of the lacrimal sac.* A few cases have been observed where a myoblastoma occurred in the lid.[3] Our case is the first instance of a myoblastoma of the brow, apparently connected with the orbicularis muscle.

Most of these tumors belong to the benign or uniform type of myoblastoma,[4] and our case also falls into this group. A malignant form has been described,[5] but its nature is dubious.

The typical tumors are usually small and grow slowly; they show no evidence of malignant growth, and there is no tendency to recur or to metastasize.

The histogenesis of the myoblastoma remains unknown. Many authors believe that it is a true myogenic tumor steming either from the striated or the smooth muscle cell. While a number of points would speak against this theory, tissue cultures of the tumor [6] have revealed characteristics which resembled cultures of various forms of striated muscle. Other authors believe that this is a neurogenic tumor. No specific cell could be found from which the myoblastoma would originate, but there is indeed usually a characteristic nerve involvement and the general structure of the tumor may simulate a plexiform neuroma. Surface epithelium and its appendages, as well as histiocytes, have been mentioned as possible germinal cells. All these theories could not change the term "myoblastoma," which is now deeply rooted in the medical terminology.

The histologic picture of this tumor is characteristic. A pathognomonic feature is the presence of fine eosinophilic granula in the cytoplasm of the tumor cell. The cell nuclei are usually small. The cells are arranged in sheets and fascicles embedded in a framework of collagen and reticulum fibers.

Our patient was a 36-year-old white man. For one year prior to his admission he noticed a lump in the outer third of his right brow. The tumor seemed to

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From the Department of Ophthalmology, College of Medicine, State University of Iowa, and the Veterans Administration Hospital.

* References 1 and 2.

grow during the last few months. The past history was irrelevant except for a blow to the right side of the face in 1944. This injury, the details of which are unknown, caused a laceration of his lid that had to be sutured. The wound healed without any after-effects.

On physical examination a 3×2 cm. long tumor was palpated under the skin of the right brow. The tumor was nontender, firm, and elastic. The skin was freely movable above it. X-ray pictures showed no bony defect.

The tumor was excised on Jan. 12, 1956. It shelled out very easily, and only in one area was it adherent to the periost of the superior orbital rim. The postoperative course was uneventful. The histologic examination revealed a typical granular-cell myoblastoma (Fig. 1). No recurrence has been noted so far.

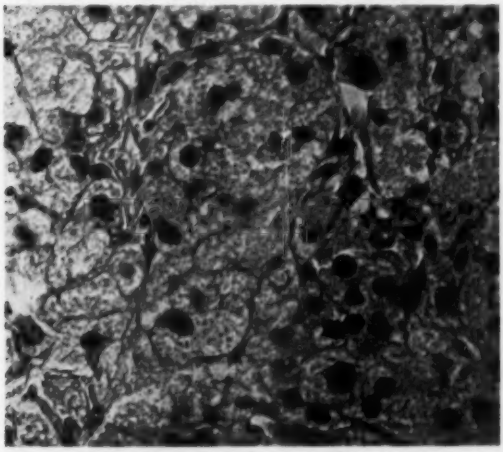

Fig. 1.—The typical cells of a granular-cell myoblastoma. The large cells are sharply outlined and have a conspicuous granula in the cytoplasm.

II. Embryonal Rhabdomyosarcoma

Malignant tumors of the striated muscles in the orbit are not frequent. They are a disease of childhood, and of 20 reported cases 16 occurred between the ages of 2 and 9, while 3 adults could be observed with this orbital tumor (in 1 instance the age was not given).[7] The frequency of this tumor is certainly much higher than these figures would indicate. It seems to be the commonest primary malignant tumor of the orbit in children.

The tumor presents itself first as a fleshy growth under the conjunctiva, or it causes a unilateral exophthalmos. Only a biopsy can give the correct diagnosis. The average age at onset is 6-7 years, and it is found twice as frequently in males as in females.[8]

The histologic picture varies with the maturity of the cell. It is very likely that some of the less-differentiated tumors are not recognized as myosarcomas and are diagnosed as round-cell or spindle-cell sarcoma. If the cells are maturer they will develop into pink-staining ribbon cells resembling muscle cells. This type of sarcoma is referred to as embryonic rhabdomyosarcoma or sarcoma botryoides. There is, however, always a great degree of polymorphism with many giant cells. A close connection with an extraocular muscle is usually appreciated. If the tumor is still more differentiated, the fibrils in the cytoplasm may show striation. This would then be the fully developed form of a rhabdomyosarcoma.

The only treatment available is exenteration of the orbit. It was originally

assumed that the prognosis is invariably poor.[9] Reese could show, however, that a rhabdomyosarcoma has a much better prognosis than any other type of orbital sarcoma. In his series [10] two out of five children were well more than 10 years after the operation. Correct diagnosis and prompt treatment are therefore mandatory.

Our patient was a 7-year-old white girl who was first treated by a local physician for a lid droop on the left side in April, 1955. A small growth beneath the nasal bulbar conjunctiva was removed. The pathologic report revealed an undifferentiated sarcoma, and the child was referred to the University Clinic. She was first seen here on May 15, 1955, and except for a fine scar in the area of the right semilunar fold extending into the upper fornix the eyes were essentially normal. The child underwent a complete pediatric, urologic, and neurologic work-up. The only positive finding was a double kidney on the left side.

The child returned on Aug. 1, 1955, with a soft pinkish tissue mass in the area of the inner canthus above the caruncle. Four days later this tumor was excised and a histologic examination showed again a malignant tumor, but this time the diagnosis of a rhabdomyosarcoma could be made (Fig. 2). It was also

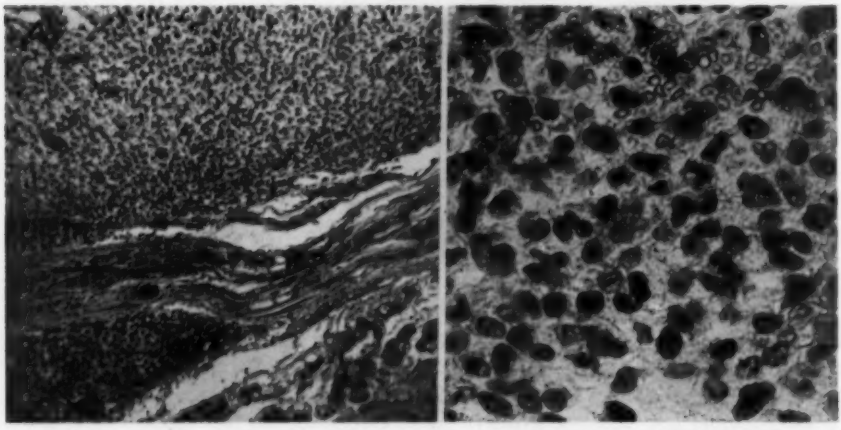

Fig. 2.—*A*, in an over-all view the close relation between the tumor and the external ocular muscle is apparent. *B*, in a higher magnification elongated ribbon cells can be seen in a highly pleomorphic tumor.

evident from the specimen that the tumor extended into the orbit along the internal rectus muscle. Therefore, three weeks later an exenteration of the left orbit was performed. Histologically, tumor tissue was found in the nasal and upper segment of the orbit. The eye was entirely normal. The postoperative course was uneventful, and on the last follow-up examination (May 10, 1956) the child was in good health and no recurrence or metastases could be found.

III. Summary

The first case described presents a typical granular-cell myoblastoma occurring in the brow. These tumors are only rarely found around the eye. They are benign, and local excision is the treatment of choice.

The second case presented is that of rhabdomyosarcoma of the orbit in a young girl. These tumors occur more frequently than is suspected and are probably

the commonest primary malignant orbital tumor in children. Early diagnosis and exenteration are the only chance for a permanent cure.

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Meningioma (Dural Endothelioma) of the Optic Nerve

Report of a Case

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and
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The purpose of this paper is to report a case of optic nerve meningioma observed in a child at age 11 years and subsequently 17 years later. Certain unusual features have seemed instructive to us. Brief mention of this case has been made elsewhere.*

Optic nerve tumors were classified by Leber in 1877 as intradural and extradural (Hudson). In 1902, Byers collected all reported optic nerve tumors. He considered them as fibromas (see Hudson). In 1912, Hudson [1] classified optic nerve tumors as gliomas, meningiomas, and fibromas. Writing in Penfield's "Cytology and Cellular Pathology of the Nervous System," Verhoeff,[2] in 1932, followed Hudson's classification. In 1938, Cushing and Eisenhardt [3] published a monograph on meningiomas and included several cases of interest in regard to the case here reported. Davis,[4] in 1939, wrote regarding primary tumors of the optic nerve and emphasized particularly the coexistence of neurofibromatosis and gliomas of the optic nerve and/or chiasm.

Occurrence and Incidence

Meningiomas that affect the optic nerves originate within the cranium, in the optic canal, or in the orbit. Forrest [5] studied 184 primary orbital tumors, and of these 17 were meningiomas. Craig and Gogela,[6] of the Mayo Clinic, found 17 meningiomas that were primary in the orbit and 35 that invaded the orbit. It is of interest that Verhoeff questioned the origin of these tumors from within the orbit while granting that such an origin might well occur. Coston's[7] case, studied in this hospital in 1936, seemed to have fulfilled the requirements of a strictly intraorbital meningioma. In those cases which are within the orbit, the origin is from the arachnoid surrounding the optic nerve. The same holds true for those that are intracanalicular. In rare instances intraorbital meningiomas may arise away from the nerve sheaths, possibly from arachnoid tufts that have come to lie outside the dura.

Meningiomas (dural endotheliomas) are most often seen in women of middle age; Hudson found such tumors in 20 females and 7 males. These tumors occur in children. Hudson reported three in patients under 10 years of age; Dandy [8] removed one in a child of 5 and earlier reported a bilateral optic nerve en-

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dothelioma in a child of 13. Offret [9] described one in a child of 3 years. Cushing and Eisenhardt described several cases in young persons. Our patient was a boy 11 years of age when he was first seen; unquestionably the tumor had been present for a long time prior to his visit to us.

Meningiomas occur infrequently in Negroes.

Pathology

Meningiomas vary widely in their microscopic appearances. A classsification offered by Craig and Gogela seems as satisfactory as any other: (*a*) meningiomatous meningioma with sheets and lobules of spindle-shaped endothelial cells; (*b*) psammomatous; (*c*) fibroblastic. The psammoma bodies probably originate from degeneration, hyalinization, and later calcification of the endothelial-cell whorls. Often pleomorphism is visible in a single slide, as Dandy pointed out.

The tumor is locally invasive but does not metastasize. Intraocular involvement has been recorded by Hudson and by Coston, among others. There may be invasion of the disc, choroid, or sclera. In some instances the tumor actually invades the optic nerve, though the pia has been given credit for blocking spread to optic nerve substance. Hudson described several cases of invasion of the nerve, and such invasion has also been described by Broendstrup,[10] Cushing, and Offret.

Meningiomas which originate within the orbit tend to spread into the cranium, and those within the cranial cavity, similarly, are apt to encroach upon the orbit.

Symptomatology

Proptosis without pain usually precedes loss of vision. Both the proptosis and the loss of vision are slowly progressive. In most instances the eye is pushed straight forward and cannot be shoved easily back into the orbit. Often there is diplopia, although the range of extraocular movements remains full in many cases. The field of vision may remain full. There is no characteristic field defect. The optic nerve is either pale or swollen. In some long-standing cases there may be edema with atrophy. Rarely, the tumor invades the retina or choroid adjacent to the nerve.

Roentgenograms may be normal. The orbital walls may be eroded. The optic foramen may be enlarged, and the canal may show erosion. The sphenoidal ridge may show hyperostosis.

Report of Case

White boy 11 years of age blind in the right eye. Tumor seemed to originate in the optic disc. Enucleation advised but rejected. Left eye normal. Seventeen years later right eye unchanged. Optic atrophy, left eye; loss of temporal field; L.E.V. 20/100. Right eye enucleated. Psammomatous meningioma of choroid, optic nerve, and optic nerve sheaths. Craniotomy. Tumor removed from around right nerve and chiasm.

The patient was first seen in the Wilmer Institute, age 11 years, with a 3-month history of blindness of the right eye. The totally blind right eye was deviated externally.

The pupils were equal in size, but the right pupil reacted only to consensual light stimulation. The ocular movements of both eyes were of full range. In the right eye a mass was seen to arise from the temporal side of the disc and there was pallor of the nasal side. The mass came forward 2 to 3 D. at its

highest part. In total area, it covered four to six times the size of the disc. There was pigment on the nasal side of the mass toward the macula. There were no hemorrhages or exudates, and no vessels were seen extending into the mass.

The left eye was normal in all regards, including visual acuity and visual fields.

The diagnosis was thought to lie between optic neuritis, congenital abnormality, and tumor. The patient was instructed to return in three months and did so. The picture was unchanged. It was advised that the patient be readmitted to the hospital for enucleation of the right eye, but he was not seen until 17 years later, when he was 28 years of age.

The patient returned with a story of failing vision in the left eye for two months. The right eye was unchanged. The fundus picture had not altered so far as could be determined from examination of the earlier note (Fig. 1). The vision in the left eye was 20/60, the disc was pale and seemed slightly

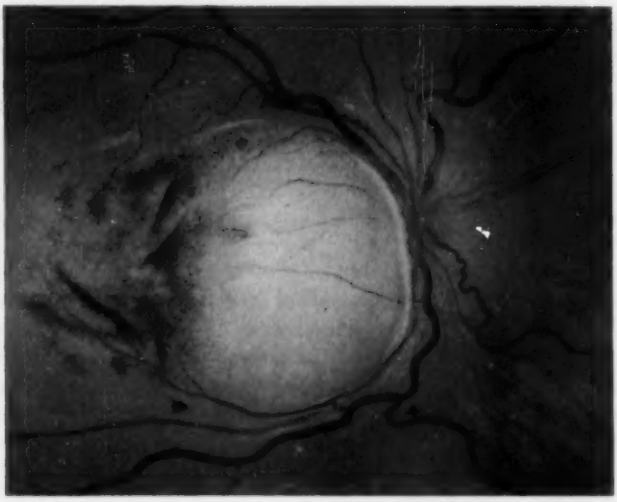

Fig. 1.—Appearance of right fundus in January, 1955.

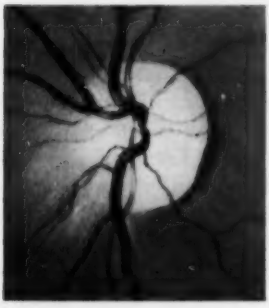

Fig. 2.—Appearance of left fundus in January, 1955.

swollen nasally (Fig. 2), and there was loss of the temporal half of the visual field. The ocular movements of both eyes remained full. With the exophthalmometer the right eye measured 18 mm. and the left eye measured 17 mm.

General physical examination revealed questionable left-sided weakness.

Roentgenograms of the skull showed sphenoidal ridge erosion. The optic

Fig. 3.—Enucleated right eye, showing involvement of the optic nerve by meningioma.

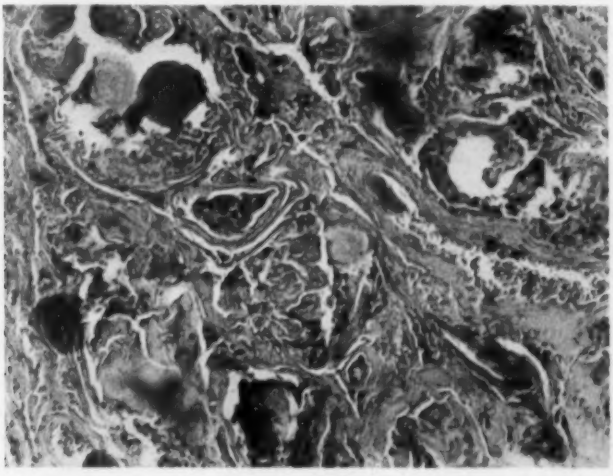

Fig. 4.—Section through tumor showing psammomatous meningioma.

foramen on the right measured 7 mm. It was slightly larger than the foramen on the left. There was no erosion of the canal wall.

On Jan. 25, 1955, the right eye was enucleated. It was obvious that there was a tumor involving the nerve (Fig. 3). This was a psammomatous meningioma (Fig. 4). The optic nerve was invaded, also the choroid (Fig. 5).

A right carotid arteriogram was made on Jan. 31, 1955. This showed a space-occupying lesion situated anteriorly in the region of the chiasm.

On Feb. 1, 1955, a right frontal craniotomy was done (Dr. George Smith). A tumor was found extending from the right optic canal. It surrounded the optic nerve and the carotid artery. It involved the chiasm and the left optic nerve. The tumor was removed insofar as possible. The bone was not touched. It was likewise psammomatous meningioma.

After operation was performed, there was a temporary diabetes insipidus. On discharge, the patient had 20/70 vision in the left eye and the upper nasal field remained.

Comment

Features of this case merit comment. 1. Meningiomas are slow-growing, as exemplified by the absence of change in the picture of the optic fundus over a period of 17 years. 2. Absence of limitation of ocular movements and the absence of proptosis with proved intraorbital tumor is of interest. Proptosis is often a prominent sign of optic nerve tumor primary in the orbit or with tumors which

Fig. 5.—Meningiomatous involvement of the choroid and optic nerve.

extend from the cranial cavity to the orbit. 3. In this case there was enlargement of the optic canal to 7 mm. According to Pfeiffer,[11] this is the upper limit of normal. From the size of the optic nerve in the orbit and the mass within the cranium, it would have been anticipated that the optic canal would be much wider than was the case. There was no demonstrable erosion of the canal wall, and so extensive tumor involvement of the optic nerve in the orbit with extension to the cranial cavity or extension from the cranial cavity to the orbit via the optic canal does not necessarily produce pronounced enlargement of the canal nor does it necessarily produce erosion. A normal optic canal does not eliminate the possibility of tumor extending through it from the orbit to the cranial cavity or vice versa. In this case the canal was not unroofed after consideration of the intracranial features of the tumor. 4. Invasion of the optic nerve by meningioma and its presence within the eye is a most unusual feature, but it is not unique.

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The Anatomy of the Trabecular Meshwork as Seen in Tangential Section

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The trabecular meshwork has a unique appearance, an important location, and it is not exceedingly small. Yet confusion and controversy still exists concerning its anatomy. This is readily understandable, for in studies of eye pathology meridional sections are made, in which only an unsatisfactory lateral view of the meshwork is seen.

In sections of the eye as usually made in the pathology laboratory, the trabeculae appear as a number of interrupted linear fibers running from the end of Descemet's membrane to the scleral spur and the ciliary muscle. This appearance is quite different than that which is seen in tangential and transverse sections and has led to disagreement on a number of points.

1. Uveal and corneoscleral trabeculae. The trabeculum is usually described as consisting of two parts: an inner nonelastic uveal portion and an outer corneoscleral part containing elastic fibers. Anderson [1] states that the absence of elastic fibers is the chief histological distinguishing factor of the uveal meshwork. To Rochon-Duvigneaud,[2] Assayama,[3] Virchow,[4] and Duke-Elder,[5] the major part of the meshwork is corneoscleral, the uveal portion being represented by a vestigial remnant of delicate trabeculae on the inner surface of the corneoscleral portion. Assayama [3] finds that the uveal meshwork usually consists of one layer, rarely two, and sometimes is absent. But to Allen, Burian, and Braley,[6] who divide the portions of the meshwork according to their anterior and posterior attachments, a large part of the meshwork is uveal. To Henderson,[7] who suggested the term "cribriform ligament" for the entire meshwork, the structure is "nothing more than an open and non-sclerosed part of the sclera, and as such consists of longitudinal and circular fibers arranged crossways as a warp and woof so as to form an open meshwork."

2. Intratrabecular openings and interlamellar spaces. The spaces between the lamellae of the meshwork have been confused with the intratrabecular openings. Cells seen between the lamellae have been interpreted as being in and plugging the intratrabecular openings. Similarly, narrowing or widening of the spaces between the lamellae of the meshwork have been spoken of as enlargements or narrowing of the intratrabecular spaces, which, of course, is not at all the same thing.

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3. Type of communication between the anterior chamber and Schlemm's canal. Anatomy of the inner wall of Schlemm's canal. Difference of opinion concerning the anatomy of the inner wall of Schlemm's canal and the way the aqueous passes through the trabeculae to the canal is great, and this divergence of opinion has recently been well catalogued by François [8] as follows:

"If some think (Schwalbe, 1870) a direct communication exists by a system of trabecular clefts, others (Rochon Duvigneaud, 1893) agree with either an osmotic process for noncolloidal substances (Friedenwald, 1936), or a diffusion process (Kronfeld, 1932), or a filtration process (Fortin, 1942), or an ultrafiltration process.

"Sondermann (1932), Theobald (1934), and Thomassen and Bakken (1951) postulated that there exists a direct communication. For Seidel (1918) the pores of the filter should have the same size as those of a collodion-membrane (three percent). One finds the same divergent opinions concerning the presence of endothelium on the level of the trabecular system, which, if it exists for some authors is absent for others.

"Even those accepting the existence of endothelium do not agree with its anatomic repartition; for Gutman (1895) it only covers the walls of the clefts, which constitute the communications between the anterior chamber and Schlemm's canal, for others it establishes an uninterrupted and nonperforated covering which is, however, not impassable (Leber, 1895) because colloidal substances can find an outlet either by slipping between the cells or by phagacytosis."

The openings between the meshwork and Schlemm's canal were described by Sondermann [9] as being relatively large openings and having an endothelial lining. From Sondermann and Theobald's [10] sections of these "inner canals," the openings appear to be 10μ to 25μ in diameter. Other investigators [11] do not find such openings. Recently François and co-workers [8] have demonstrated by microradiographic techniques that the "pores" in the inner wall of Schlemm's canal are of a size between 1μ and 2μ. Huggert,[12] of Stockholm, using injections of chromium phosphate particles and bacteria of various sizes, also found the pores to be 1μ to 2.5μ in size.

Wolf [13] has been impressed by the tissue in the area immediately adjacent to Schlemm's canal on the trabecular side. He described it, from ordinary meridional sections, as resembling cotton wool. He believes that this tissue is homologous with the tissue under the endothelium of an arachnoidal villus and speculates that the trabecular meshwork functions in the same way as does an arachnoidal villus. In the picture in his book, the "cotton wool tissue" is much thicker than is usually seen. He states that here elastic tissue is absent. This is, incidentally, the area in which Teng, Paton, and Katzin [14] found most of the degeneration in their study of aging and glaucomatous eyes.

Recognizing that tangential views were essential for study of the anatomy of the meshwork, Assayama,[3] Rochon-Duvigneaud,[2] and Virchow [4] at the turn of the century made histologic studies of tangential sections of this structure. They made their preparations by immersing the eye in water and teasing the meshwork loose from the eye with dissecting needles and then examining the entire meshwork on a slide. With this crude technique much was learned of the real anatomy of the meshwork.

Believing that sections made from meshworks which had been teased from the eye would fail to give all of the relationships of the meshwork and might show considerable distortion, I made efforts to produce tangential sections of

the meshwork in situ. To my knowledge no one has previously reported descriptions of the anatomy of the meshwork as seen in tangential sections made in situ.* A. Ray Irvine Jr.† has been studying tangential sections of the trabeculae made in situ since 1951, with particular emphasis on the changes in the meshwork in glaucomatous eyes.

Materials and Methods

As part of a study of the structure and function of the trabecular meshwork in normal and glaucomatous eyes, the trabecular meshwork of 16 apparently normal eye bank eyes, 8 eyes enucleated because of neoplastic disease, and 12 eyes with early open angle glaucoma have been examined in serial tangential sections made in situ. In this paper the appearance of meshworks of eyes with "normal" angles only will be described. The trabeculae of the glaucomatous eyes are still being studied, and the findings will be reported at a later date.

The eyes were obtained from the Stanford Eye Bank and from unused callottes of the Stanford Eye Pathology Laboratory and the Armed Forces Institute of Pathology. More than 700 microscopic slides of the meshwork have been examined.

The first preparations were made from specimens already prepared in pyroxylin (Celloidin) by cutting down from the outside of the eye in serial section completely through the meshwork until the anterior chamber was reached. Good tangential sections of the trabeculae were obtained by this method.

Since the meshwork is on the inner surface of the limbus, it was realized that by starting to cut the sections from the anterior chamber surface fewer sections would be needed to encompass the entire meshwork and Schlemm's canal. Accordingly, such sections were made and were quite satisfactory.

Because of the equatorial curve of the eye, however, these sections, like the ones made by the previous method, had only a small amount of the meshwork on any one slide. It was found that with gentle pressure this curve could be partially flattened, with no distortion of the anatomy and yet with much more of the meshwork present on a single slide. Comparison of meshworks prepared by all three methods reveal no difference in the appearance of the trabeculae with any of the three methods used. This last method was then adopted because of its obvious practical usefulness; it is done as follows:

A section of wet tissue 2 to 3 mm. on each side of the limbus and 10 to 20 mm. in length is cut parallel to the limbus. This strip of tissue, which, of course, has the meshwork along its entire length is placed in melted paraffin with the inner surface down. It is then gently compressed from above with a flat instrument. The bottom of the pan is cooled rapidly with ice, and the compressing weight is removed. Serial sections are then made from within, outwards. Alternate slides were stained with Masson's trichrome stain. A variety of stains, including hematoxylin and eosin, periodic acid-Schiff, and Verhoeff's elastic stain, were used on the remaining slides.

Results

Viewed tangentially, the trabecular meshwork is seen to be strikingly more complex than when seen meridionally. Controversy over what is uveal mesh-

* Since the time this paper was written, a report by Ashton and co-workers has been made in the *British Journal of Ophthalmology*, 40, No. 5 (May) 1956, describing somewhat similar sections of the meshwork.

† Irvine, A. R., Jr.: Personal communication to the author.

work and what is corneoscleral is easily resolved, for the uveal and corneoscleral meshworks are seen in tangential section to have quite distinct anatomical features.

Traced in serial sections from the anterior chamber outwards to Schlemm's canal, three areas with distinctly different histologic characteristics are seen (Fig. 1): (*a*) the uveal meshwork (the inner lamellae); (*b*) the corneoscleral meshwork (the middle and largest portion); (*c*) the inner wall of Schlemm's canal, the "pore tissue."

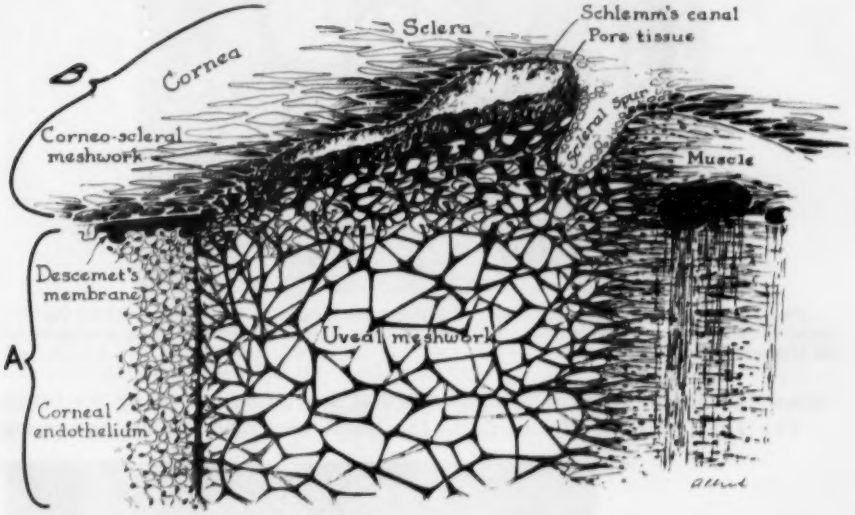

Fig. 1.—Lower one-half of diagram (*A*) shows appearance of the uveal meshwork from within the anterior chamber. In the upper part of the diagram (*B*) the meshwork and Schlemm's canal have been cut obliquely, almost transversely, to show all of the lamellae and their relations to the scleral spur and the ciliary muscle.

(*a*) *The Uveal Meshwork.*—In all of the eyes studied the uveal meshwork was always present; indeed, its appearance was so striking and characteristic that it served as a landmark of use in locating the meshwork on the slide. The uveal meshwork consists of the inner one or two lamellae. A lamella consists of a meshwork of small beams lying in a single plane. Each beam is circular in cross section and is made up of a central core of collagen fibers covered by an endothelium containing cells with flattened nuclei. The average diameter of a uveal beam is 4μ. The beams are arranged to form large irregular spaces frequently trapezoidal or rhomboidal in form (Fig. 2). These openings are irregular and have no definite orientation. Their size varies from 25μ to 75μ across. The large elliptical nuclei with prominent nucleoli, which have been described as endothelial cells, lie outside the collagen core which makes up the bulk of the beams. These nuclei closely resemble the fixed cells of the sclera and cornea. A barely visible transparent tissue, as seen with Masson's stain, covers the collagen beams.

Each uveal lamella is attached on one side to the tissue at the end of Descemet's membrane (Schwalbe's line) and on the other side to the ciliary muscle, principally the longitudinal fibers (Fig. 2).

Occasionally a uveal lamella courses posteriorly to attach to the iris, to form an iris process. In every case in which a connection between the trabecular

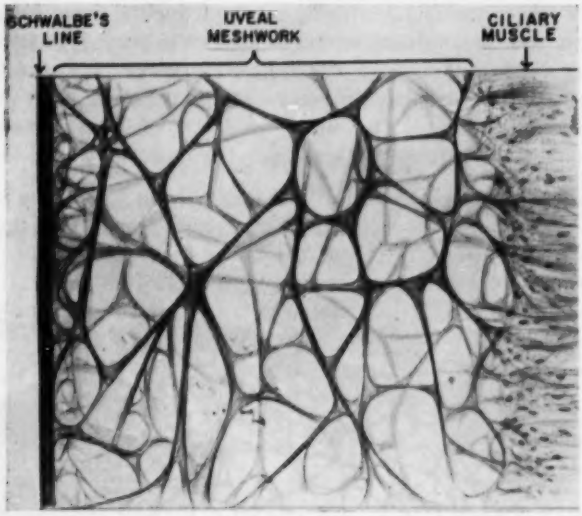

Fig. 2.—Diagram of one lamella of the uveal meshwork in tangential section, showing attachments. Note the characteristic angular openings, which frequently assume a rhomboidal or trapezoidal form.

area and the iris was present the tissue was that of uveal meshwork, not iris tissue.

(*b*) *The Corneoscleral Lamellae.*—The beams are broad and flat, measuring

Fig. 3. — Photomicrograph of the uveal meshwork in tangential section. Compare with Figure 2.

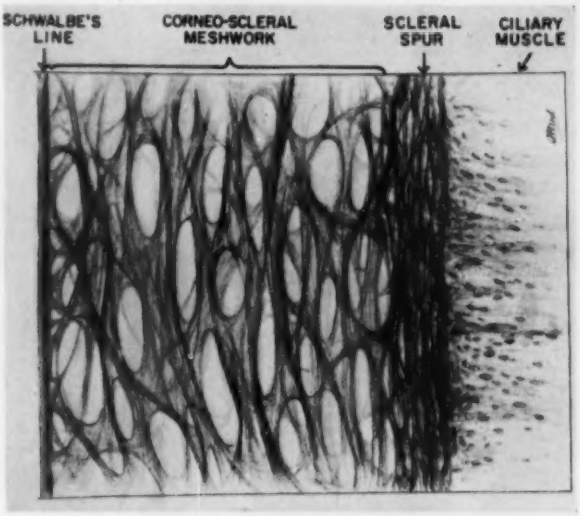

Fig. 4.—Diagram of one lamella of the corneoscleral meshwork in tangential section, showing attachments. Note that the course of the meshwork fibers and of the long axis of the openings is parallel to the scleral spur and perpendicular to the longitudinal fibers of the ciliary muscle which attaches to the scleral spur.

$3\mu \times 7\mu$ to $3\mu \times 20\mu$ in cross section. Each beam is seen to be made of a number of collagen fibers which run in an equatorial direction (Figs. 1 and 4). This

Fig. 5.—Photomicrograph of corneoscleral meshwork. Note the elliptical openings, the long axes of which run in an equatorial direction.

is perpendicular to the direction in which the fibers appear to be coursing in ordinary meridional sections. The beams of the inner lamellae are broader than the outer ones.

Numerous elliptical openings are seen with the long axis of the openings

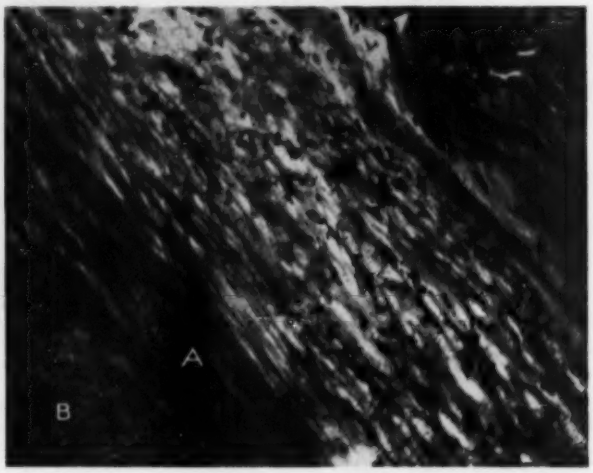

Fig. 6.—Photomicrograph of corneoscleral meshwork. Note the scleral spur (*A*) and the ciliary muscle (*B*).

parallel to the direction of the fibers (Figs. 4, 5, and 6), i. e., in an equatorial direction. Assayama [3] in 1901 noted the elliptical shape and equatorial orientation of these spaces in his study of teased trabeculae.

This direction is also seen to be parallel to the fibers of the scleral spur

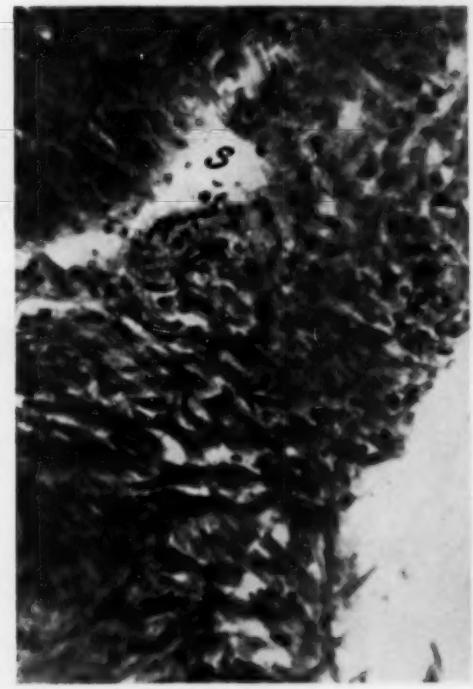

Fig. 7.—Photomicrograph of oblique section through the meshwork. The arrows point to cut sections of corneoscleral trabeculae. The trabecular beam closer to Schlemm's canal (*S*) is considerably smaller than the inner one. *P* marks the "pore tissue." Compare with Figure 1, *B*.

and to be perpendicular to the longitudinal fibers of the ciliary muscle, which may be seen attaching to the scleral spur (Figs. 4, 5, and 6). From the orientation of these openings it would seem that contraction of the ciliary muscle would make the openings rounder and therefore larger. This point is now being investigated by Dr. Christian Zweng and myself in monkey eyes.

The size of the elliptical openings varies in each lamella, but, like the beams (Fig. 7), the openings are somewhat smaller in the outer lamellae than in the inner ones. The average size of these elliptical openings is about $10\mu \times 30\mu$, but many are as small as $5\mu \times 15\mu$ and some are as large as 15μ to 50μ. They are always smaller and show less variability in size and shape than the openings in the uveal meshwork.

The lamellae are attached on one side to Schwalbe's line and the deep corneal stroma and on the other side chiefly to the scleral spur. The deepest lamellae may sometimes continue posterior to the spur to attach directly to the meridional fibers of the ciliary muscle.

Occasionally anterior-posterior beams are seen which seem to be connecting one lamella to the lamella immediately adjacent to it, but these interlamellar beams are uncommon. In transverse sections they are hard to find. Assayama [8] states that in teased preparations of the meshwork one can separate and remove the lamellae one at a time.

The lamellae are usually 8 to 14 in number and are farther apart near the ciliary body and scleral spur (Fig. 8). On the other side, close to their attach-

Fig. 8. — Photomicrograph of ordinary meridional section. The lamellae are farther apart near the ciliary muscle and are closer together near Descemet's membrane. Note the irregular arrangement and thickness of the "pore tissue."

ment to Schwalbe's line, the lamellae in meridional section appear densely packed and are difficult to count. Endothelial cells attach to the surface of the collagen beams just as they do in the uveal meshwork. Because nuclei are present on both surfaces of each beam, there may appear to be, in meridional section, a greater number of lamellae present than is truly the case.

The appearance of the corneoscleral trabeculae varies greatly with the age of the person. In children and young persons the collagen component is much less and the endothelium is more prominent (Fig. 9). Indeed, in the young the endothelium may obscure some of the openings so that the typical elliptical-shaped

openings, although present, are harder to find. In older persons the increase in collagen, apparently at the expense of the endothelium, makes the anatomy of the openings in the meshwork more easily seen.

Fig. 9. — Photomicrograph of corneoscleral meshwork of a 10-year-old boy. There is less collagen in the beams; consequently, the pattern of the elliptical openings is harder to discern. Note the scleral spur (*A*) with the fibers of the ciliary muscle (*B*) running perpendicular to it.

(*c*) *The Inner Wall of Schlemm's Canal (the "Pore Tissue").*—I have traced in serial tangential sections the size of the openings in the uveal and corneoscleral meshworks from the anterior chamber to Schlemm's canal and have found, as I have already described, that until the region of the inner wall of Schlemm's canal is reached the openings are much larger than the 1μ to 2μ pore size demonstrated by François and co-workers[8] and Huggert.[12] The small openings of 1μ to 2μ, the pores, must therefore be in the region of the inner wall of Schlemm's canal. This tissue I shall call the "pore tissue."

If Schlemm's canal is lined by a single layer of endothelium which lies on the outermost lamella of the corneoscleral meshwork, then this endothelium must be adherent to this trabecular lamella. For if it were not attached, this very thin membrane would collapse with the slightest increase in pressure in the anterior chamber. What is the nature of this attachment, and what is the anatomy of the tissue in this area?

The tissue between the innermost corneoscleral lamellae and Schlemm's canal is difficult to study in tangential section. The inner wall of Schlemm's canal is very irregular, having frequent, sometimes angular, outpouchings into the lumen of the canal (Fig. 8).

In oblique and transverse sections one can see that the inner wall of Schlemm's canal is adherent to the outermost corneoscleral lamella by thin collagenous strands of tissue. There is a great concentration of nuclei in the "pore tissue." These nuclei appear identical with those in the corneoscleral and uveal beams. The distance between the nuclei is variable. The appearance of the internuclear tissue is variable, being sometimes fibrillar, sometimes glassy (Fig. 10). It seems to be made up of the same tissue which is the outer layer of the trabecular beams.

There is great variability in the thickness of this tissue in different persons and in different areas in the same person. In young persons the "pore tissue"

is thinner. In some older persons the tissue in some areas become as much as 10 times its usual thickness of 5μ to 7μ (Fig. 8).

In my opinion, the endothelial-lined inner canals described by Sondermann [9] as direct communications between the anterior chamber and Schlemm's canal are artefacts. In tangential sections no such structures are seen. The openings of the canals as pictured by Sondermann [9] and Theobald [10] are too large, being in the neighborhood of 10μ to 25μ.

One can speculate on the nature of the direct openings in Schlemm's canal. It is possible that the great concentration of nuclei in the inner wall, which have the same appearance as the nuclei of the meshwork, represents the nuclei of the same endothelial tissue which is around each beam of the meshwork. The relative

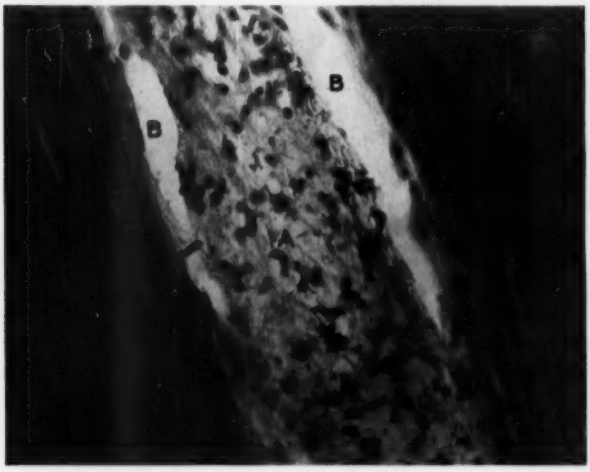

Fig. 10. — Photomicrograph of a tangential section of an outpouching of the inner wall (*A*) of Schlemm's canal into the canal itself (*B*). Note irregular, sometimes fibrillar, sometimes glassy appearance. The nuclei are arranged in an irregular fashion.

amount of endothelial tissue in comparison to collagen is greatly increased, and so the endothelium surrounding a single collagen fiber may be in contact with the endothelium surrounding the next fiber, with no spaces being present as they are in the meshwork itself. The fluid, under pressure, would pass through by slightly indenting and squeezing between the endothelial membranes. Openings of the small size of 1μ to 2μ could be better explained in this way than by an endothelium-lined canal, which would have to have a lumen less than one fourth the size of a capillary. The linear shape of some of the openings in the inner wall described by François [8] could also be explained by this hypothesis. The outpouchings and thickenings found in some areas of the inner wall might be caused by localized increased resistance in these areas. The nature of the "pore tissue" must be investigated further, however.

Summary

To understand the anatomy of the trabecular meshwork, study of tangential sections of this structure is essential. A method of making tangential sections of the meshwork in situ is described. From tangential sections, traced serially from the anterior chamber to Schlemm's canal, three areas with distinctly different anatomic structures are seen: the uveal meshwork, the corneoscleral meshwork, and the inner wall of Schlemm's canal. The appearance of these structures is

described, including the size, shape, and orientation of the openings in the uveal and corneoscleral trabeculae.

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Ocular Manifestations of Riley-Day Syndrome

Familial Autonomic Dysfunction

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In a series of papers, the first of which was published in 1949, Riley * and his co-workers have described a syndrome, called familial dysautonomia, which is becoming of increasing interest to both the pediatrician and the ophthalmologist. Since the syndrome has been defined only in recent years, there are relatively few cases on record. Nevertheless, it is probably not a rare disease. Dr. Riley † knows of more than 70 cases which meet his criteria.

The syndrome is characterized by a plethora of symptoms. The earliest manifestations in infancy may be retarded development with low weight gain, difficulty in swallowing, and frequent bouts of respiratory infection or aspiration pneumonia with an exaggerated febrile response. The infant is subject to dehydration and may perspire and drool excessively. He fails to produce tears when he cries. The reported cases have occurred in Jewish children, with a few exceptions. The physical examination reveals generalized indifference to pain, including corneal hypesthesia; hyporeflexia; labile hypertension, and postural hypotension.

The purpose of this paper is to present a more complete picture of the ocular manifestations of familial dysautonomia (Riley-Day syndrome). Three cases are reported which represent different degrees of corneal involvement. Case 1 represents the severe ulcerative type. In this case, the postmortem findings including the ocular pathology are recorded for the first time. Dr. David Cogan made the pathological report, and his findings are quoted verbatim below. Cases 2 and 3 are presented as examples of the minimal, easily overlooked, and more frequent types of keratopathy not previously described.

Case 1.—A Jewish boy was born at the Beth Israel Hospital on Jan. 30, 1951, weighing 5½ lb. He was in medical difficulty almost constantly until his death, two years later. On the second day of life he developed otitis media and diarrhea with leucocytosis. He was treated with penicillin and sulfadiazine. Oxygen was used continuously for the first few days and intermittently for the next 19 days. After discharge from the hospital he became a feeding problem at home and failed to gain in weight. He developed diarrhea and was admitted to the Children's Medical Center on April 29, 1951, at the age of 3 months. Neurological examination showed evidence of some gross cerebral defect, and there was a poor corneal reflex in each eye. X-ray studies revealed double renal

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From the Massachusetts Eye and Ear Infirmary, Department of Ophthalmology, Harvard Medical School, and the Children's Medical Center.

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† Riley, C. M.: Personal communication to the author.

pelves and ureters. He responded fairly well to general supportive therapy, but he subsequently had to be readmitted to the Children's Medical Center, in May and November, 1951, for bronchopneumonia and continued failure of normal development. A diagnosis of pancreatic fibrosis was considered. A single stool trypsin test was negative. During the third hospitalization, when the child was 8 months of age, the right eye became congested. Ophthalmologic examination at first revealed a fairly large abrasion in the center of the right cornea. Local antibiotics, cortisone, and pressure bandages were recommended, but regeneration of the corneal epithelium failed to occur in the usual manner. On the contrary, the corneal lesion became progressively more extensive and deep. The cornea assumed a bluish-white, milky appearance. There was no ciliary congestion. It was then noted that the corneas were almost completely anesthetic and dry. There was definite hypesthesia in the distribution of the fifth cranial nerve. A Schirmer test showed marked deficiency in tear formation, and the child was observed to cry without tears. I thought the child had a neuroparalytic keratitis. Dr. Trygve Gundersen and Dr. Joseph Clough agreed, and they suggested a tarsorrhaphy. This procedure was then carried out on the right eye by Dr. Clough, who treated the child until its death. During the course of this admission, copious drooling, tongue biting, and generalized indifference to painful stimuli were noted. At this time, the diagnosis of familial dysautonomia was made by Dr. William Berenberg, who made the diagnosis in Cases 1 and 2.

After the patient's discharge from the hospital, the tarsorrhaphy produced considerable improvement in the ulceration of the right cornea. When the cornea no longer stained with fluorescein, the lid adhesions were divided. Soon, however, a diffuse opacity appeared in the lower third of the left cornea. At this time the patient was seen in consultation at the Massachusetts Eye and Ear Infirmary, where it was thought that the indolent ulceration and keratinization of the cornea in a relatively white eye were most suggestive of vitamin A deficiency, secondary to pancreatic fibrosis. Figure 1 is an artist's drawing from a Kodachrome ‡ of

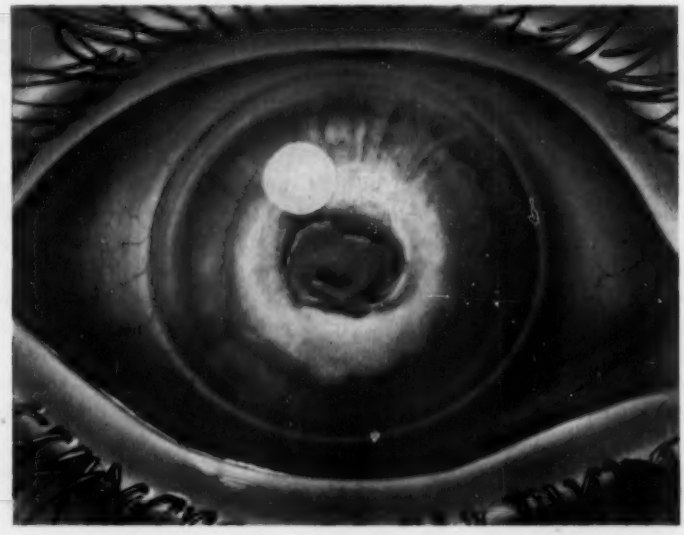

Fig. 1 (Case 1).—Artist's drawing from Kodachrome film, showing dense, deep, and diffuse involvement.

the right eye modified to show the appearance of the right cornea before the tarsorrhapy. Because of the ulceration of the left cornea, the child was admitted to the Children's Medical Center for a fourth time, on Jan. 18, 1952, for lid suturing of the left eye. During this admission, the question of vitamin A deficiency was investigated. An oral vitamin A-absorption test was normal. After his discharge from the hospital, the child was observed as an outpatient until January, 1953, when the left cornea again became ulcerated. The patient was then admitted to the Massachusetts Eye and Ear Infirmary on two occasions, both for more extensive tarsorrhaphy on the left eye. During the course of these hospitalizations, a dermatology consultant stated that, in his opinion, there was no clinical evidence of vitamin A deficiency. On one occasion, the child developed a temperature of 108 F secondary to otitis media. His tongue biting became so serious that multiple tooth extractions had to be carried out. On March 9, 1953, without warning, he was found dead in his crib.

An autopsy was performed, and the general pathologic diagnoses were as follows: bronchopneumonia confluent, bilateral, extensive; lacerations of the tongue; bilateral double ureters and pelves, and multiple tooth extractions. The pancreas was normal.

The following is the verbatim report of Dr. Cogan's description of the microscopic ocular pathology: Right eye: eye normal except for cornea. This shows

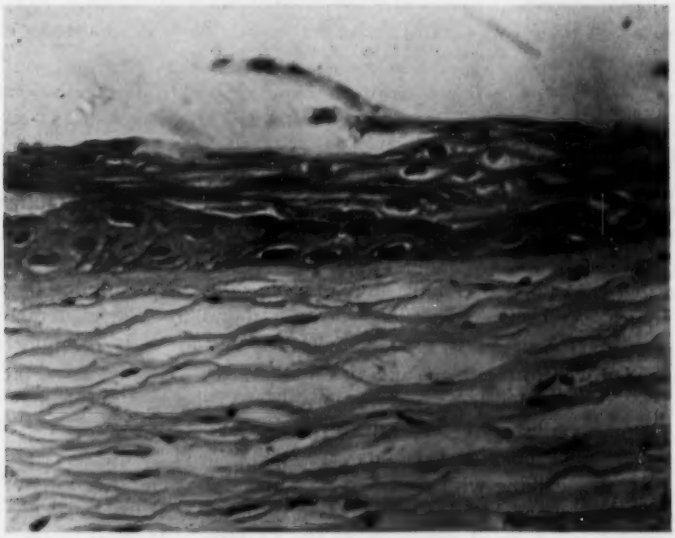

Fig. 2 (Case 1).—Photomicrograph of hematoxylin-and-eosin-stained section of cornea, showing metaplasia and keratinization of epithelium.

definite metaplasia of epithelium with some keratinization (Fig. 2). In one area, there is band keratopathy with a plaque that is becoming exteriorized. Beneath the epithelium and especially beneath the calcified plaque, the superficial stroma is very loose and shows some increase in cellularity with round cells and a few blood vessels. Bowman's membrane is only occasionally present. Sudan staining

‡ The stereo Kodachrome photographs were taken by Dr. David Donaldson. The drawings were made by Mr. William Stenstrom.

is negative, but von Kossa stain is positive. No goblet cells are seen in the conjunctiva, but this may not be abnormal.

Left eye: The corneal epithelium of this eye looks essentially normal, although it is peculiarly separated from Bowman's membrane in one area. However, the superficial stromal lamellae appear abnormally fine (such as one finds in the conjunctiva), suggesting a rarification of the preexisting collagen or the formation of new fibers that have not yet developed collagen. In other areas Bowman's membrane appears thin, suggesting the former. The changes in this eye, unlike those in the other eye, suggests that the primary abnormality is in the superficial corneal stroma.

Comment.—This is an example of ocular involvement in familial dysautonomia (Riley-Day syndrome) so severe that it resembles neuroparalytic keratitis and keratomalacia. It is very much like those cases reported by Dunnington [4] and also like the two cases reported by Segall [5] as "congenital neuroparalytic keratitis." Pancreatic fibrosis with secondary vitamin A deficiency and keratomalacia can produce a similar picture, both in its systemic and in its ocular manifestations. In this particular case, most of the criteria for familial dysautonomia were present. The postmortem findings were nonspecific, but this is not surprising in a disease which is thought to be due to a disturbance of neurologic function. Autopsy was useful, however, in ruling out pancreatic fibrosis. The microscopic examination of the ocular tissues was also nonspecific in its findings, merely showing the evidences of severe keratinization and ulceration with an absence of inflammatory reactions.

Case 2.—A Jewish girl was born on Nov. 27, 1949. The gestational period and delivery were uneventful, and the birth weight was 5 lb. 5 oz. Almost from the beginning she began to have intermittent bouts of atelectasis, pneumonia, and diarrhea over a period of four months. After discharge from the hospital, there occurred several episodes of bronchitis. She was first admitted to the Children's Medical Center on Jan. 4, 1951, at 13 months of age. Two or three days prior to admission, she developed a fever which rose progressively to 106 F, associated with noisy breathing and vomiting. She was treated with penicillin, without much effect. On admission, she was found to have moderately severe dehydration and pneumonitis. It was felt that she also was mentally retarded. She responded well to treatment and was discharged seven days later, on January 11, 1951. She was admitted again on July 8, 1953, because she had never been known to tear while crying, had had numerous breath-holding episodes, had cyanosis, exhibited emotional lability and generalized indifference to painful stimuli, and was walking with considerable clumsiness. The diagnosis of familial dysautonomia was made at this time by Dr. William Berenberg. There were no ocular complaints. A third admission to the Children's Medical Center occurred on Feb. 6, 1955, because of high fever and severe dehydration. On admission, she was found to have ocular involvement. Examination of the cornea revealed a fairly large horizontally elliptical area of epithelial edema, confined to the region covered by the lower lid. Approximately the lower one-fourth of the cornea was involved, and there was a more widespread diffuse haziness of the underlying corneal stroma extending upward to the midpoint of the cornea. There was no actual ulceration. Both eyes were completely white and quiet, and the corneas showed marked hypesthesia. There was also definite hypesthesia of the face in the distribution of the fifth cranial nerve. Although the child did not cry with

tears, the eyes did not actually seem dry at the time of this or subsequent examinations. Since the lesion appeared to be in the area of the cornea which might be exposed during sleep and because of the corneal hypesthesia, deficiency in lacrimation, and severe dehydration, isotonic saline was instilled in both eyes at frequent intervals from the time of admission. This resulted in definite improvement in the appearance of the cornea. Frequent instillations of ophthalmic borid acid ointment were also advised. Although the corneal lesions improved considerably, the photograph shown in Figure 3, taken after discharge from

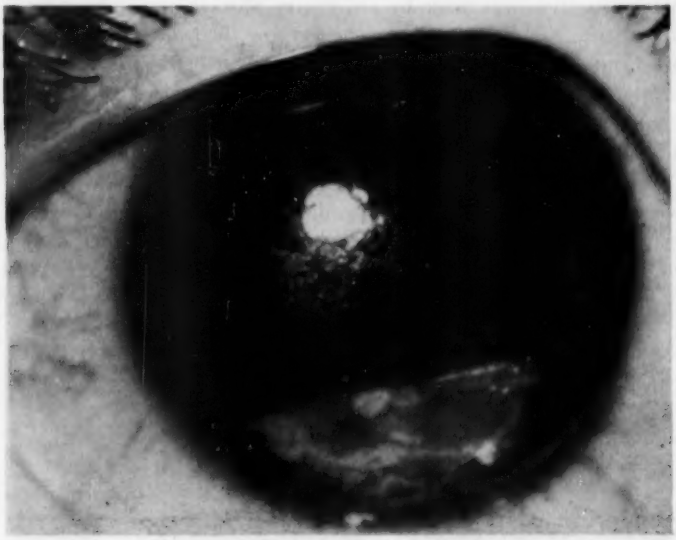

Fig. 3 (Case 2).—Black and white reproduction of actual photograph (Kodachrome) of right eye almost at the height of its involvement. Only a faint scar can be seen at present (similar to Case 3, Fig. 4).

the hospital, shows that considerable corneal pathology was still present. Subsequently, the epithelial lesions healed, leaving well-defined elliptical superficial scars which were obvious for seven months. At the present time, even these scars have faded considerably, but they can be seen easily with focal illumination and low magnification. The parents have been instilling a bland ointment into each eye every night and have been advised to do this three times a day if and when bouts of fever and dehydration occur. There have been no further attacks of acute corneal involvement during the year in which the patient has been under my observation. The visual acuity is 20/25 in each eye.

Comment.—The corneal involvement in this case is clinically different from that in Case 1, where the involvement was more central, more ulcerative, and more milky-white in appearance. In this case, the involvement was almost entirely in the lower one-third of the cornea and the lesion responded very readily to simple local treatment. The residual scarring is minimal and could easily be overlooked on casual examination. Nevertheless, when active, the lesion was very obvious, but it could never have been confused with keratomalacia or neuroparalytic keratitis.

Case 3.—A Jewish boy was born normally at full term and weighed 6 lb. 1½ oz. His first admission to the Children's Hospital was at age 3½ months,

on June 9, 1952, because of failure to gain in weight. Past history revealed that he had been hospitalized elsewhere when 3 weeks of age for bronchitis, requiring steam and chlortetracycline (Aureomycin) treatment. A neurologic consultant felt the child showed some evidence of mental retardation; subsequently, he was admitted to the Children's Hospital a total of 19 times! The majority of these admissions were for bronchopneumonia, tonsillitis, and pharyngitis with hyperpyrexia and dehydration. He failed to gain in weight and was underdeveloped. Between the fourth and fifth admissions, the diagnosis of familial autonomic dysfunction was made by Dr. Harry Shwachman. This time it became apparent that the child failed to tear when crying, had diminished pain sensation and marked emotional lability, and was retarded in both motor and intellectual development. The child was examined by numerous members of the resident and visiting staff during these 19 admissions. Ocular involvement was never noted. I saw him on Aug. 3, 1955, when he was 3 years old. Definite irregular superficial scarring in the lower one-fifth of the right cornea and faint scarring of the left cornea were observed. These scars seemed to be at the level of Bowman's membrane, some of them being linear and some of them roundish in shape. Only the lower one-fifth of each cornea was involved. There was definite hypesthesia of both corneas. Figure 4 is an artist's drawing of the Kodachrome picture.

Fig. 4 (Case 3).—Artist's drawing from Kodachrome film of right eye. The lesion is exaggerated for purposes of illustration and can actually be seen only with a loupe (2 × magnification).

Comment.—This case is an example of the minimal type of corneal involvement in which ocular symptoms do not necessarily come to the attention either of the parent or of the pediatrician but are observed only in ophthalmologic examination, with use of focal illumination with magnification. Such lesions are important diagnostically and therapeutically. They indicate that the corneas are vulnerable and suggest that prophylaxis, in the form of a protective ointment, instilled at night, is indicated.

Summary

Three cases are presented which represent different degrees of corneal involvement in Riley-Day syndrome (familial dysautonomia). The ocular abnormality may consist of the following:

(1) A severe central ulceration resembling neuroparalytic keratitis and keratomalacia, responding only to tarsorrhaphy.

(2) A mild process resembling exposure keratitis in its location and appearance, responding readily to the instillation of a protective bland ointment or to saline eye drops.

(3) A faint scarring resembling etched glass in the lower cornea occurring in the absence of any history of ocular symptoms or disease.

The clinical photographs in these cases were taken by David D. Donaldson, Howe Laboratory of Ophthalmology, Boston.

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In Vivo Studies on the Choroidal Circulation of Rabbits

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The choroidal circulation has presented a challenging problem to investigators who have attempted to determine its basic physiology. Few attempts have been made to study this rich vascular coat of the eye, and the approach to the problem has varied. The opaque sclera in higher animals has been a constant obstacle to the external approach to these vessels. Only recently have reports appeared of observations made by means of the external approach to determine the response of the choroidal vessels to various chemical and nervous stimuli.*

Emphasis has been focused on this vascular coat of the eye in recent years by the anatomic contributions of Ashton[4] and Wybar.† Many ocular diseases may be attributed directly or indirectly to choroidal vascular disease. The role of the choroid in the problems of glaucoma, sympathetic ophthalmia, the Sturge-Weber syndrome, choroideremia, and retinal detachments, along with a variety of other pathologic ocular processes, remains to be clarified. Ashton,[4] in 1952, stated: "After more than two centuries of careful research it is remarkable that our information upon some of the essential points should remain so inadequate."

Because of the paucity of experimental reports available on the reactions of the choroidal vessels, this investigation was undertaken in an attempt to develop and utilize a practical method for direct observation of the choroidal circulation and, through it, to study the effects on the choroidal vessels of some of the commonly employed drugs. After preliminary experiments to determine the best means of studying the choroidal circulation, we considered that the excellent view afforded by dehydration of the sclera would best serve our purposes.

Procedure

Albino rabbits varying in weight from 2 to 5 kg. were chosen. The absence of uveal pigment in the albino rabbit facilitates study of the choroidal

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Fellow in Ophthalmology, Mayo Foundation (Dr. Stein); Section of Physiology (Dr. Wakim) and Section of Ophthalmology (Dr. Rucker), Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

* References 1-3.

† References 5 and 6.

circulation by the afore-mentioned technique. In contrast to man, the venae vorticosae of rabbits lie considerably anterior to the equator ‡ and hence may be seen by this technique. Rabbits are also well suited for this method because the supraorbital ridge lies behind the equator of the eye and hence a large segment of the anterior portion of the eye can be viewed. Pentobarbital (Nembutal) sodium in doses of 25 to 30 mg. per kilogram of body weight was given intravenously as the anesthetic agent in all experiments.

With the anesthetized rabbit secure in a conventional rabbit box (Fig. 1),

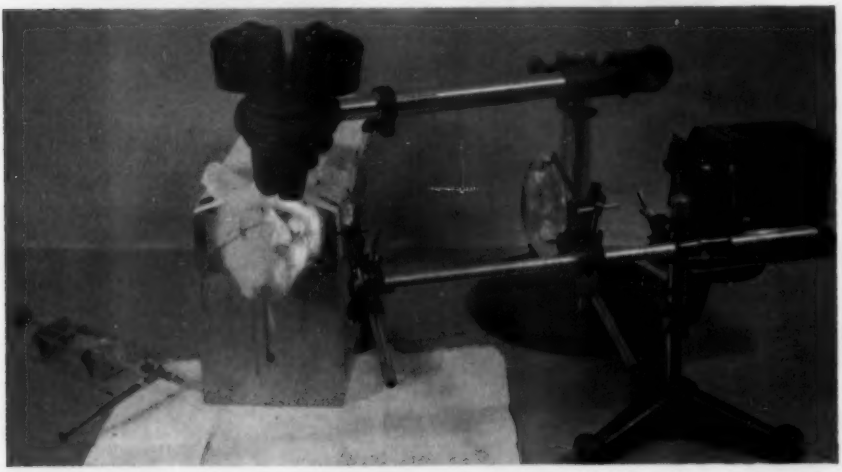

Fig. 1.—Apparatus set up for observation of the choroidal vessels in the eye of the albino rabbit.

00 black nonabsorbable surgical (silk) sutures were inserted into the palpebral conjunctiva of the upper and lower lids near their margins for retraction sutures. The lids were retracted, and the eye was exposed. Medial and lateral canthotomies were performed to permit more adequate exposure of the eye. In some cases in which the level of anesthesia was not sufficiently deep, 0.5% solution of tetracaine (Pontocaine) hydrochloride was instilled and 1% solution of procaine hydrochloride was injected at the canthi. The nictitating membrane was drawn forward and excised to allow greater exposure of the medial portion of the eye.

The conjunctiva and bulbar fascia were drawn taut and incised in a curved incision 2 mm. behind and parallel to the limbus, in the superior nasal section of the globe. The conjunctiva and bulbar fascia were dissected free from the underlying sclera as far posteriorly as exposure permitted. In some cases, a 0000 silk suture was inserted in the tendon of the superior rectus muscle to aid in this procedure. The conjunctiva and fascia were then retracted with 0000 silk sutures. This exposed an area of sclera measuring approximately 13 by 10 mm. in the superonasal quadrant of the globe.

As the result of dehydration produced by exposure of the bared sclera to room air, transparency of the sclera began to occur, accompanied in about five minutes by reddening under the sclera (Fig. 2). Within 15 to 20 minutes, the

‡ References 7 and 8.

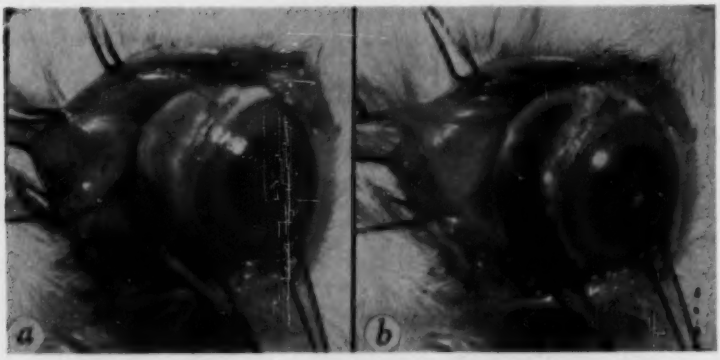

Fig. 2.—(*a*) Lids retracted, with conjunctiva incised at limbus and pulled back to expose underlying sclera. (*b*) Fifteen to twenty minutes after exposure to air, the sclera becomes dehydrated and transparent.

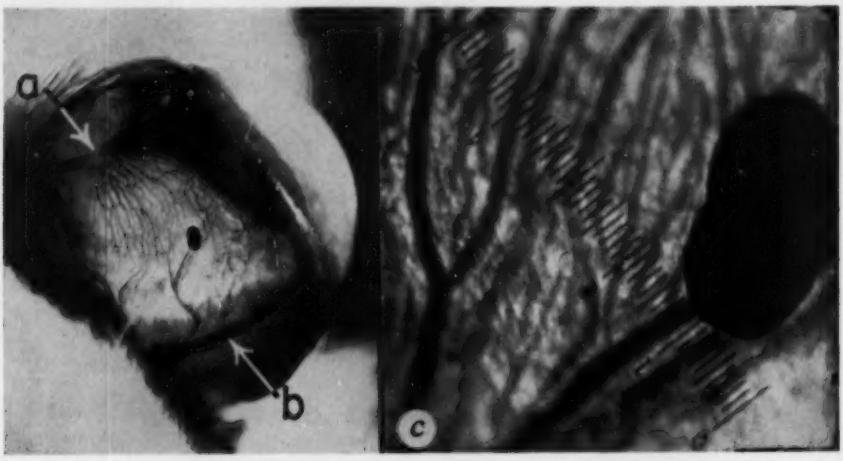

Fig. 3.—(*a*) and (*b*) Direct transillumination through the pupil, demonstrating the vascular network in the choroid. (*a*) One of the venae vorticosae. (*b*) Long posterior ciliary artery. (*c*) Photomicrograph of choroidal arteries in same rabbit. Ink mark has been placed on sclera to identify choroidal artery. Each unit on scale corresponds to 30μ; reduced slightly from mag. × 40.

opaque sclera in the exposed region became completely transparent, thus providing a clear view of the underlying vessels (Fig. 3). The transparent sclera could be made opaque again within a few minutes by covering it with the retracted conjunctiva and upper lid. This procedure was repeatedly reversible.

A relatively cool light, from the use of thick glass lenses with intervals of air, was used as a source of illumination (Fig. 1). By means of two convex lenses, light from a 300-watt projector was focused through the pupil of the rabbit's eye. Thus, the choroidal vessels could be viewed from an external approach by transillumination from the light that filled the interior of the eye.

For viewing the scleral vessels, a wide-field binocular microscope was set up over the transparent exposed portion of the sclera (Fig. 1). The magnifica-

tions used in this study were × 60 and × 90. A micrometer scale was inserted in one of the oculars and standardized with a Bausch and Lomb micrometer disk so that each small unit on the scale corresponded to 25μ at × 60 and 18μ at × 90. For photography, a special monocular microscope of × 40 was used, with a micrometer scale on which each small unit corresponded to 30μ. Serial photomicrographs were taken every 10 to 15 seconds as confirmation of the many observations made and recorded. With this arrangement, an excellent view of the choroidal vessels and blood flowing through them could be obtained, and direct measurement of the caliber of the vessels could be made.

Drugs previously warmed to body temperature in a water bath were administered by means of a fine polyethylene tube into either the vein of the ear or the common carotid artery on the same side as the eye being examined. In parallel studies on albino rabbits of similar weights, determinations of blood pressure were recorded by means of a strain-gauge manometer connected to the femoral artery.

Observations on the choroidal vessels were made continuously before, during, and after injections; with the aid of a stop watch, recordings of the caliber of vessels were made as early as changes were apparent and at 1-minute intervals for 30 minutes. We usually selected a small choroidal artery whose connection with the long posterior ciliary artery could be definitely established. An India-ink mark was placed on the sclera overlying one of the smaller choroidal arteries of a caliber of 50μ to 75μ (Fig. 3). This ink mark was placed 6 to 8 mm. behind the limbus and consequently behind the equator of the rabbit's eye, which is 5.5 mm. from the limbus according to Urrets Zavalia.[9] The ocular containing the micrometer scale was turned so that one of the units of the scale was placed against one edge of the vessel wall for measurement of the diameter of the choroidal artery before, during, and after administration of the various drugs employed. This method permitted continuous observation of the comparative diameters of the same cross section of the selected vessel under various conditions.

Results

Under low-power magnification, the long posterior ciliary artery, varying in size from 200μ to 360μ, could be seen coursing toward the limbus in the anterior portion of the eye (Fig. 3). Superiorly, one of the venae vorticosae could be seen that was located 4 to 5 mm. behind the limbus and that measured about 450μ in diameter at its origin. The larger channels entering the vortex averaged about 230μ in diameter. Lying between this vein and the long posterior ciliary artery, numerous small channels could be seen, many of which were fed by branches of the long posterior ciliary artery. These vessels varied in size from 18μ to 90μ, with by far the majority being about 50μ to 75μ in diameter. Under high-power magnification (× 90), the flow of blood was visible in these choroidal vessels.

Effect of Drugs Given Intravenously.—Sodium nitrite in doses of 2 mg. per kilogram of body weight was injected into the veins of the ear of five rabbits. The diameters of the observed vessels ranged from 36μ to 100μ. This drug produced no detectable change in caliber of the choroidal arteries.

Epinephrine hydrochloride (1:1000) was administered intravenously to 10 animals, with repetition in 3 animals, making a total of 13 observations. The dose ranged from 2γ to 40γ per kilogram of body weight, the usual dose being 10γ per kilogram. The caliber of the vessels examined ranged from 50μ to 100μ,

with an average of 63μ. Vasoconstriction of the observed artery occurred after all 13 injections. From the average preinjection caliber of 63μ, the arteries constricted to an average of 49μ (Fig. 4). This represents a net change of 22%.

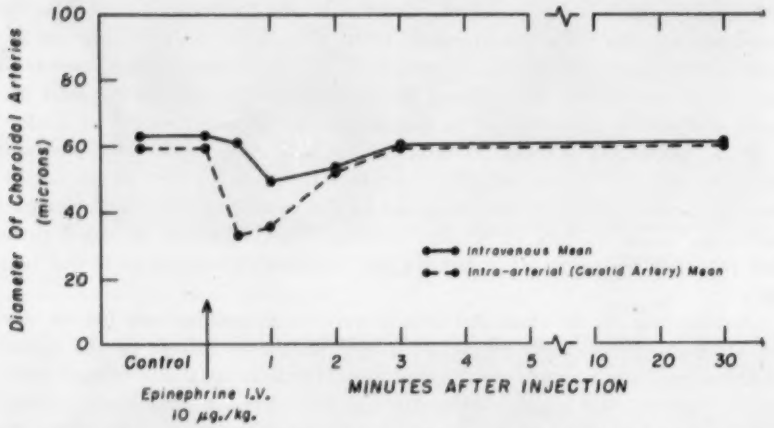

Fig. 4.—Comparison of the changes produced in the caliber of the choroidal arteries by intravenous and by intra-arterial injection of epinephrine. Vertical arrow indicates time of intravascular injection.

In addition, blanching of the entire field appeared, indicating transient reduction in blood flow in the underlying choriocapillaris. The blood flow increased about a minute after the injection of epinephrine. The blood pressure underwent a maximal increase of 65 mm. of mercury systolic at about 30 seconds, with return to the control value within 2 minutes.

Nicotinic acid was administered in doses of 1 mg. per kilogram of body weight to 10 rabbits. Choroidal arteries ranging in caliber from 36μ to 100μ were observed continuously for the regular period of 30 minutes, but no change in their diameter could be detected. In one animal nicotinic acid doses of 25 and 50 mg. per kilogram given intravenously failed to produce any detectable change.

Histamine diphosphate in doses of 90γ per kilogram of body weight was administered intravenously to eight rabbits, with repetition in two. Choroidal arteries ranging in diameter from 36μ to 100μ were observed. No detectable changes occurred in the caliber of the vessels measured. In one case, a dose of 675γ per kilogram was used (seven and a half times the usual amount). Death occurred at the end of four minutes, but detectable changes in caliber of the vessels did not occur during continuous observations prior to death.

Ergotoxine was administered intravenously in doses of 165γ per kilogram of body weight to nine rabbits. Choroidal arteries ranging in diameter from 36μ to 100μ were observed. No change in caliber of the choroidal arteries was noted. One animal received 0.5 mg. of ergotoxine per kilogram, which represented three times the usual amount, but no changes in the choroidal arteries could be detected.

These various effects are summarized in the accompanying Table.

Effect of Drugs Given Intra-Arterially.—In order to obtain a more concentrated solution and a direct action on the choroidal arteries, the afore-mentioned five drugs, previously warmed in a water bath to 37 C, were administered

Effect of Intravenous and Intra-Arterial Administration of Various Drugs on Choroidal Vessels of the Rabbit

Drug	Av. Dose/per Kg.	Intravenous Injection			Intracarotid Injection		
		Animals, No.	Observations, No.	Effect on Choroidal Arteries	Animals, No.	Observations, No.	Effect on Choroidal Arteries
Sodium nitrite	2 mg.	5	5	No change	5	5	No change
Epinephrine	10 γ	10	13	Vasoconstriction	6	11	Vasoconstriction
Nicotinic acid	1 mg.	10	11	No change	4	4	No change
Histamine diphosphate	90 γ	8	10	No change	4	4	No change
Ergotoxine	165 γ	9	9	No change	4	5	No change

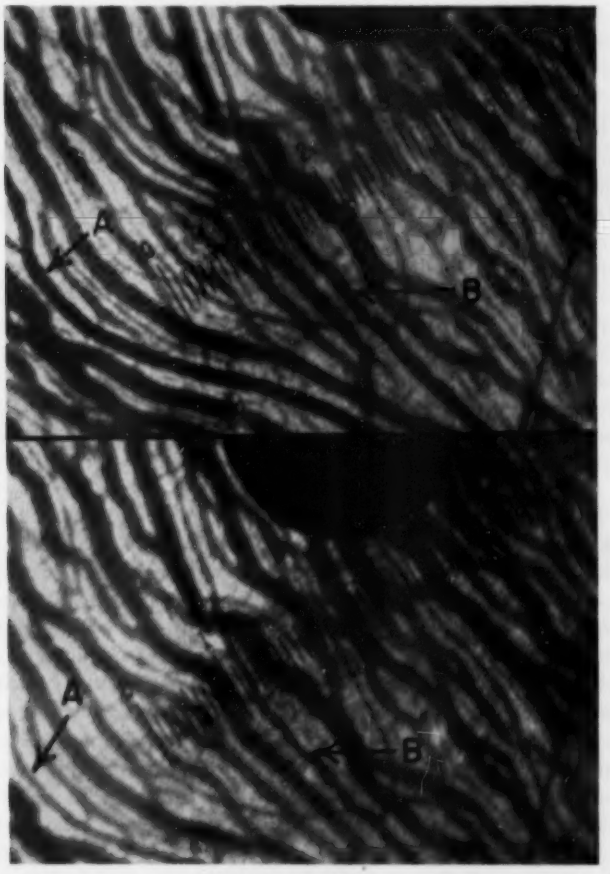

Fig. 5.—Upper panel shows choroidal arteries prior to intra-arterial injection of epinephrine. The vessels marked *A* and *B* each measure 45μ in width. Lower panel shows the same field one minute after intra-arterial injection of epinephrine. Note vasoconstriction of the choroidal arteries. Vessel *A* is reduced from 45μ to 25μ, and vessel *B* is reduced from 45μ to 30μ; × 40.

through a cannula inserted into the common carotid artery on the side of the eye being observed.

Sodium nitrite in doses of 2 mg. per kilogram of body weight was thus administered to five rabbits. The vessels observed ranged in diameter from 50μ to 87μ. No effect on the caliber of the choroidal arteries was detected.

Epinephrine in doses ranging from 6γ to 20γ per kilogram of body weight, with an average dose of 10γ, was administered intra-arterially 11 times to six rabbits. Choroidal arteries ranging in diameter from 36μ to 87μ, with an average of 59μ, were observed. Within the first 30 seconds, pronounced vasoconstriction occurred (Fig. 5). The maximal changes in the caliber of the choroidal arteries occurred at 30 seconds, the average caliber being reduced to 33μ; this represents a net change of 44%. This degree of vasoconstriction was still present at the end of one minute. The caliber gradually returned to preinjection values in three minutes and remained there until the end of the observation period (Fig. 4). Intra-arterial injection of epinephrine produced blanching of the entire choroidal background, indicating severe reduction in blood flow in the choriocapillaris. One minute after intra-arterial injection there appeared an increase in the rapidity of the flow through the choroidal vessels. A maximal increase in blood pressure of 90 mm. of mercury occurred at 50 seconds, with full recovery about 2 minutes after injection.

Nicotinic acid was administered intra-arterially in doses of 1 mg. per kilogram of body weight to four animals. The choroidal vessels observed ranged in diameter from 50μ to 76μ. No changes in caliber of the choroidal arteries were detected.

Histamine diphosphate in doses of 90γ per kilogram of body weight was administered intra-arterially to four rabbits. The control caliber of the choroidal arteries ranged from 50μ to 100μ. No changes in caliber of the choroidal arteries were detected.

Ergotoxine was administered intra-arterially in doses of 165γ per kilogram of body weight to four rabbits, with repetition in one. The caliber of the choroidal arteries observed ranged from 36μ to 100μ. No changes in caliber were detected.

These effects are also summarized in the Table.

Review of the Pertinent Literature

Bothman and Cohen,§ in 1927, and Matteuci,[12] in 1946, reported on observations of the choroidal vessels by funduscopic examination with the Gullstrand ophthalmoscope. Zwiauer and Bornschein,‖ in 1949, viewed the fundi of albino rabbits through a contact lens with a Zeiss microscope in which an ocular scale was inserted. They noted that instillation of epinephrine produced pallor of the fundus and caused dyes that previously had been injected intravenously to remain longer than normally in the choroidal vessels. However, they were unable to detect any changes in caliber in the choroidal vessels but did observe changes in caliber of the retinal vessels induced by use of epinephrine, vasopressin, amyl nitrite, and glyceryl trinitrate (nitroglycerin).

The external approach to the study of choroidal circulation was first introduced by Leopold,[1] in 1951, who inserted scleral windows in albino rabbits that permitted a direct view. A Barkan light directed through the pupil transilluminated the choroidal vessels. By this external approach, the view of the vessels was

§ References 10 and 11.

‖ References 13 and 14.

independent of any changes in the pupil that occur so frequently with the various drugs and nervous stimuli used and that make ophthalmoscopy difficult. At that time, he observed no effects with a large variety of drugs instilled topically, intravitreously, and intravenously. In a recent motion picture and in personal communications to us, Leopold ¶ stated that epinephrine given topically, intravitreously, and intravenously produced vasoconstriction of the long and short posterior ciliary arteries.

Ashton [4] referred to Cook's work on scleral windows in viewing the choroidal vessels in living rabbits and published a photomicrograph, but so far no report of this work has appeared in the literature.

Vilstrup,# in 1952, injected a polyester of resin into both carotid arteries simultaneously in living rabbits. This solidified in 30 seconds, forming a cast of the choroidal vessels and resulting in death of the animal. Using this technique, she was able to compare the effects of epinephrine, pilocarpine, and histamine instilled locally in one of the eyes with the condition of the untreated eye. After enucleating both eyes and comparing the plastic-filled choroidal vessels under the microscope, she found no changes in caliber of the vessels in eyes treated with epinephrine and pilocarpine. Local use of histamine, however, caused pronounced dilatation of the capillaries and arterioles of the choroid.

The ability of the sclera to become transparent has been known for some time, but little has been written about it. As early as 1875, Leber * noted transparency of the sclera occurring in persons who were dehydrated as the result of cholera. Fischer [17] sought to investigate the red patches in the sclera that had been observed incidentally by Kahn [18] while doing spectroscopic studies through the fundi of proptosed eyes of rabbits. Fischer found these red patches to be choroid shining through the sclera. In an extensive biochemical analysis of the sclera, he demonstrated that the transparency of the sclera necessary to observe the red spots could be explained by local dehydration. By evaporation or by use of hypertonic solutions of such substances as citrate or sugar, he was able to dehydrate the sclera through the intact conjunctiva until it became transparent. This transparency was a reversible phenomenon that was affected by hydration or by loss of water.

Greaves and Perkins,[2] in 1952, noted this same phenomenon while carrying on studies on the aqueous veins of rabbits. After removal of the conjunctiva, a stream of warm air was directed on the bared sclera until dehydration occurred. Using the microscope of the Haag-Streit slit lamp, with a droplet of oil on the sclera, they studied the choroidal vessels directly with a beam of light shining through the pupil and found that an excellent view of the choroid could be obtained. They noted lightening of the color of the background when epinephrine was given intravenously and also with sympathetic stimulation; they stated that this change presumably was caused by constriction of the choroidal capillaries. Perkins,[3] in 1954, reported on the vasomotor innervation of choroidal vessels observed through dehydrated sclera by this same technique and similarly concluded that sympathetic stimulation produced vasoconstriction.

Comment

The external technique that we used for observation of the choroidal circula-

¶ Reference 15; Leopold, I. H.: Personal communication to the authors.

References 7 and 16.

* Leber, T., cited by Leopold.[1]

tion was similar in many respects to that of Greaves and Perkins,[2] in which the opaque sclera is rendered transparent by dehydration. This technique in albino rabbits permits the selection of isolated arterial branches of the choroidal vessels that can be observed continuously through a binocular microscope containing an ocular scale. It also permits the taking of rapid serial photomicrographs to substantiate the findings.

The rapid and transient measurable vasoconstriction of the choroidal arteries that we noted after intravenous administration of epinephrine, together with the pronounced blanching of the background indicating reduction in the blood flow in the choriocapillaris, is in accordance with the afore-mentioned findings of others. These include the observations of Bothman and Cohen,† the pallor of the fundus and delayed disappearance of dye noted by Zwiauer and Bornschein,[13] the vasoconstriction of the long and short posterior ciliary arteries noted by Leopold,‡ and the lightening of the background noted by Greaves and Perkins,[2] all of which changes were noted after intravenous injection of epinephrine.

Search of the literature disclosed no studies on the caliber of choroidal vessels after intracarotid injection of drugs. As already noted, intra-arterial (carotid) studies, while not of much practical importance, permit a higher concentration of the drug and a more direct action on the choroidal vessels.

The degree to which the drugs used in our study influenced the underlying capillary bed could not be directly determined, as the choriocapillaris is not accessible to direct observation and measurement. As noted with epinephrine, changes in the choriocapillaris could be only inferred by blanching of the color of the background.

The choroidal vascular effects of intravenously injected epinephrine reached their peak in one minute and lasted for about three minutes, with a net change of 22%. Epinephrine given intra-arterially reached its peak effect earlier, within 30 seconds, and lasted about 3 minutes, with a net change of 44%. It would appear from our studies that epinephrine given intra-arterially (carotid artery) exerts a stronger as well as an earlier vasoconstrictive effect on the choroidal arteries than does epinephrine given intravenously.

Summary

Dehydration and consequent transparency of the sclera were induced in the eyes of albino rabbits by retracting the lids and incising and retracting the conjunctiva. This led to visibility of the underlying choroidal vessels. By means of a binocular microscope containing an ocular scale, a choroidal artery was identified by a small ink mark on the overlying sclera. This easily reproducible method of external examination of the choroidal circulation was utilized in observing and recording with serial photomicrographs any changes in caliber of the choroidal arteries produced by administration of vasoconstrictor and vasodilator drugs.

Epinephrine given intravenously produced measurable constriction of the choroidal arteries and blanching of the choriocapillaris. Epinephrine injected directly into the carotid artery on the same side produced similar effects, which occurred earlier and were more pronounced than were those following intravenous injection. Administration of nicotinic acid, sodium nitrite, histamine diphosphate, and ergotoxine, both intravenously and intra-arterially, even in high concentrations produced no detectable changes in caliber of the choroidal arteries.

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‡ Reference 15; Leopold, I. H.: Personal communication to the authors.

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An Evaluation of the AO H-R-R Pseudoisochromatic Plates

A Test for Detecting, Classifying, and Estimating the Degree of Defective Color Vision

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The AO H-R-R (Hardy-Rand-Rittler) Pseudoisochromatic Plates[1] present for general use a comprehensive, inexpensive, and rapid test of color vision suitable for office, school, and clinic—a test which should be of considerable practical value. The principles underlying the test and its unique features have been described in previous papers published in the ARCHIVES[2] under the title "The H-R-R Polychromatic Plates." The present paper is a brief report on our evaluation of the H-R-R Plates as made commercially available by the American Optical Company. The report will deal only with the test as a device for analyzing red-green vision, since the number of subjects who have made errors in the blue-yellow series of plates is too small to warrant conclusions as to the value of the plates of this series.

In the previous paper an evaluation was given of the H-R-R Polychromatic Plates (hereafter to be referred to as the Prototype H-R-R) as a device for detecting, classifying, and estimating the degree of defective red-green vision. The Prototype H-R-R did not, however, have general application, as it had been produced in a limited edition and copies were available only to its authors and a few cooperating laboratories and testing stations. However, the survey made by us, comparing the results of this test with those obtained from a battery of other color-vision tests on a group of 630 normal and 150 red-green defective subjects, strengthened our original conviction that a series of plates of this kind would meet a practical need. For example, the survey showed us that it was possible with the Prototype H-R-R to determine quickly not only the presence of a red-green anomaly and its type but also the degree of the defect. The latter diagnosis has value, since those whose color defect is mild were found to be capable of making the color judgments required in certain situations and vocations. Arrangements were made, therefore, with the American Optical Company to produce an edition of the test, to be called the AO H-R-R, which would be available for general use.

The H-R-R test employs symbols in pairs which, for the typical types of defect (e. g., protan, deutan), are pseudoisochromatic with their neutral background. In successive plates these symbols are presented in graded steps of chroma. In

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this way the test is designed not only to indicate the degree of the anomaly but also its type at any level of defect. The new edition was planned to incorporate improvements in the design and arrangement of the symbols and their background and to eliminate certain contour clues that occasionally interfered with clear-cut diagnosis in the Prototype H-R-R.

It was agreed with the American Optical Company that on completion of the new printed edition it was to be evaluated by the authors of the test to ensure that the colors and values as reproduced were properly adjusted and that color vision ratings obtained with the AO H-R-R compared favorably with those obtained with the Prototype H-R-R. This evaluation has been conducted as planned by the three authors of the test.* The results obtained have led to our approval of the new edition. It has also been approved by the Subcommittee on Color Blindness Studies of the Inter-Society Color Council. The test has been available for distribution since April, 1955.

Evaluation of the AO H-R-R

As was done with the Prototype H-R-R, the evaluation of the AO H-R-R covered the three aspects of the test: as a screening device to separate those with defective red-green vision from those with normal color vision and as a device to classify the type of defect (qualitative diagnosis) and to indicate the extent of defect (quantitative diagnosis).

The AO H-R-R Test as a Screening Device

On this aspect of the test we present the results of a survey made of the population of a small private school for boys. All school grades were included in the survey, and almost the entire school membership was tested. The number given the test was 154. The range in age was from 12 to 18 years. As was done with the Prototype H-R-R, we in general accepted the Revised Selection of AO Pseudoisochromatic Plates, approved by the ISCC Subcommittee on Color Blindness, as providing an adequate device for screening those with defective red-green vision from those with normal color vision. This selection of 18 plates had already been studied by us in conjunction with a large battery of color tests,[3] and when administered in accordance with the instructions it provides an acceptable separation of the two groups with the following interpretation of error score: Incorrect response to four or fewer plates indicates normal red-green vision; incorrect response to five or more plates indicates defective red-green vision. However, in the few cases where three or four plates were failed, the precaution was taken to administer an additional screening test of the pseudoisochromatic type: either the Ishihara (fifth edition), allowing incorrect response to three or fewer plates to indicate normal red-green vision,[4] or the Boström-Kugelberg, allowing incorrect response to two or fewer plates. On the basis of these criteria, 143 boys had normal color vision and 11, or 7.14%, had defective red-green vision.

While the percentage of color-defective subjects screened out in this small sample is somewhat lower than is obtained with the AO Revised Selection in larger samples, it falls within the variations found in groups previously tested by us in secondary and vocational schools in New York City. Out of a total number of 1105 such school boys, the percentage classed as color-defective by

* The senior author of the test, Dr. L. H. Hardy, died April 14, 1954.

this test equalled 7.69%. This, in our opinion, shows good agreement with the usual statement that about 8% of males in an unselected population have defective red-green vision. In larger surveys than ours and using different criteria, Waller[5] (N=9049) found 8.01%; von Planta[6] (N=2000) found 7.95%; Schmidt[7] (N=6863) found 7.75%; Nelson[8] (N=1338) found 8.82%; Farnsworth, Sperling, and Kimble[9] (N=1440) found 9.79%, and Pickford[10] (N=2000) found 7.8%. More sensitive tests and criteria could of course be used which would throw some of the less sensitive normals (often called "low normals") into the color-defective class, and thus the percentage to be called color-defective would be raised. It is our opinion that the AO Revised Selection is sufficiently sensitive to meet the current statistical criterion of color normality and color deficeincy and that it provides an adequate screening test for the detection of defective red-green vision.

The AO H-R-R test was also administered to the 154 boys comprising the present sample, with the following results. 1. All subjects rated as having normal color vision by the AO Revised Selection made no errors in reading the low chroma plates which form the screening series of the AO H-R-R when both test and retest were considered, as is allowed by the instructions. These subjects were therefore rated as having normal red-green vision by both tests. 2. The 11 subjects rated as having defective color vision by the AO Revised Selection made some errors in the screening series of plates of the AO H-R-R test and were thus rated by the latter test also as color-defective.† Therefore, our results show that the AO H-R-R, as was the case with the Prototype H-R-R, screens subjects with defective red-green vision from those with normal color vision in almost complete agreement with the AO Revised Selection.

Using other criteria, Sloan and Habel,[11] in a recent publication, did not find as clear-cut a separation between normal and color-defective subjects with the AO H-R-R as we found. In this report they compared results obtained by three commercially available pseudoisochromatic tests with those of "an experimental test composed of 20 of the more highly diagnostic plates selected from four different American and European tests." No data are given as to what percentage of an unselected population fails this 20-plate test. Therefore, we do not know if their test would screen out a larger or a smaller segment of the population than that which is currently considered to have defective red-green vision. Among the 100 subjects classified as having normal color vision by Sloan and Habel, 2 failed one plate of the AO H-R-R test. This is a situation we have not encountered. Of the 44 subjects classified by them as color-deficient who were tested on the AO H-R-R, four made no errors. At least three of these cases, however, had passed one or more of the other pseudoisochromatic tests under study by Sloan and Habel and probably belong in the doubtful or borderline group where there is no generally accepted standard of differentiation. All who have tested large samples of the population are plagued by the occasional cases who fail some screening tests and pass others and who often do not retest reliably. At present it is a matter of individual interpretation which of these sub-

† Eleven color-defective subjects is of course too small a number from which to conclude that the two tests agree in rating as to color deficiency. However, in our larger group of 97 color-defective subjects, to be discussed in the next section, this agreement was also found with but one exception. This one subject was rated by the AO H-R-R as normal and by the AO Revised Selection as color-defective (Tables 1 and 2).

jects are to be classed as borderline normal and which as borderline color-defective.

Aid in classifying such cases is sometimes sought from other performance tasks, but such tasks have for the most part not been studied as to individual differences and the range of performance given by those of all ages and intelligences who have normal color vision. In the task presented by the Farnsworth-Munsell 100-Hue test, for example, interest and attention as well as color vision play a role in the performance. While grouping of errors along certain color axes indicates anomalous color vision, a record showing scattered random errors, most of which are two-cap transpositions, is difficult if not impossible to interpret as indicative of color deficiency with our present knowledge of performance on this test. In any event, it may be said of these cases that the defect where present is of slight extent and would be apt to be a handicap to the subject only in specialized color work. Sloan and Habel seem to have had a high percentage of these mild or borderline cases in the group of 44 to which they administered the screening plates of the AO H-R-R test, at least as compared with our group of 97 color-defective subjects. That is, of our subjects only 5.2% failed one or fewer plates in the screening series while as many as 13.6% of their subjects failed one or fewer. Further, of our subjects only 21.6% failed two or fewer plates of the screening series while 34.1% of their subjects failed two or fewer.

Sloan and Habel do not discuss the other two aspects of the AO H-R-R test except to say in a footnote, "The fact that this test also gives information as to the type and degree of defect makes it more generally useful than any other pseudoisochromatic test." Our evaluation of the test in these two aspects is given in the following section.

The AO H-R-R Test as a Device to Classify Type of Defect and to Estimate Degree of Defect

The Prototype H-R-R has already been shown[2] to be highly reliable as a device to classify type of defective red-green vision as compared with other tests designed for this purpose, including the Nagel anomaloscope, and also as a device to estimate degree of defect as compared with available tests of different degrees of difficulty. Therefore, our purpose here is primarily to compare the qualitative and quantitative diagnoses given by the AO H-R-R and the Prototype H-R-R.

These two tests were administered to a group of 97 subjects with defective red-green vision. About one-third of the group had previously been studied in our laboratory on a large battery of tests,‡ which included the Prototype H-R-R. To these only the AO H-R-R was given for comparison with their earlier records. The remaining subjects were new cases, for whom a shorter battery of tests was used. In about one-half of the new cases the battery consisted of the anomaloscope, the Farnsworth Dichotomous test (Panel D-15), the resistor color code test, and the following pseudoisochromatic tests: AO H-R-R, Prototype H-R-R, AO Revised Selection, and Ishihara (fifth edition). The remaining new

‡ This battery of tests is described in Reference 2. It included the Prototype H-R-R, the AO Revised Selection, the Ishihara test (fifth edition), the Nagel anomaloscope (Model I), the Navy lantern (New London model), the color threshold tester (School of Aviation Medicine model), the Farnsworth dichotomous test (Panel D-15), and other tests as indicated in the individual case.

TABLE 1.—*Comparison of Qualitative Diagnoses Obtained from the Two Editions of the H-R-R Test (AO and Prototype)*

Prototype H-R-R	AO H-R-R Normal	AO H-R-R Unclassified	AO H-R-R Deutan	AO H-R-R Protan	Prototype H-R-R Totals
Unclassified	1*	8	1		10
Deutan		4	51		55
Protan				32	32
AO H-R-R Totals	1	12	52	32	97

*This case, which is the one referred to on page 738, failed the AO Revised Selection and the Prototype H-R-R but passed the AO H-R-R. In their report Sloan and Habel refer to a second instance of disagreement between the two versions of the H-R-R test. This second case is not considered here, because retest on the AO H-R-R classified the subject as normal on this test as well as on the Prototype H-R-R and the AO Revised Selection.

cases were given only the four pseudoisochromatic tests. All tests utilizing pigment stimuli were administered under the Easel Lamp, color temperature 6750 degrees K.

The results obtained on these 97 subjects are given in the Tables. Table 1 shows for the AO H-R-R and the Prototype H-R-R the qualitative diagnosis of type of red-green anomaly (unclassified, protan, deutan), and Table 2 shows the quantitative diagnosis of the anomaly (mild, medium, strong). In both Tables the vertical columns show the ratings of the AO H-R-R and the horizontal rows show the ratings on the Prototype H-R-R. Numbers in boxes represent subjects rated in the same category by both editions of the test.

In Table 1 can be seen the strong agreement between the qualitative diagnoses obtained by the two editions. There was no conflict between the classifications as to deutan or protan type. The few subjects listed outside the boxes

TABLE 2.—*Comparison of Quantitative Diagnoses Obtained from the Two Editions of the H-R-R Test (AO and Prototype)*

Prototype H-R-R	AO H-R-R Normal	AO H-R-R Mild	AO H-R-R Medium	AO H-R-R Strong	Prototype H-R-R Totals
Mild	1*	27	1		28
Medium			25	4	29
Strong			7	32	39
AO H-R-R Totals	1	27	33	36	97

*See footnote to Table 1.

all had a mild red-green anomaly either unclassified as to type or of the deutan type. Unclassified subjects, it will be remembered from earlier publications, are those who made errors only in the low chroma plates, which form the screening series of the H-R-R test, but no errors in the succeeding plates, which form the diagnostic series.

Table 2 gives the comparison of the quantitative diagnoses obtained from the two editions of the test. Again it will be seen that there is strong agreement between the classifications as to degree of defect by the two editions. Since within each of the series of plates for quantitative diagnosis there is some gradation in chroma, a feature which is necessary to insure qualitative diagnosis in all cases, we recognize that there must be gradations of defect within each of the three groups (mild, medium, strong) we have perhaps arbitrarily established. The few subjects listed outside the boxes in Table 2 are probably borderline between mild and medium or medium and strong, as the case may be.§

In both Tables 1 and 2 the agreement shown between the two editions of the H-R-R test is of the same order as the test-retest reliability already shown for the Prototype H-R-R.[2]

The classifications of type and extent of color anomaly listed in these Tables illustrate the twofold analysis of defective color vision that is a unique feature of the H-R-R Pseudoisochromatic Plates. Unlike pseudoisochromatic tests in prior usage, the H-R-R test goes beyond the mere separation of those with defective color vision from those with normal color vision. With the AO H-R-R Plates it should be possible to establish agreement between the qualitative and quantitative ratings yielded by the test and the color requirements of specific color tasks which involve the use of surface colors. Applications of the test to vocational selection and guidance would then have practical value.

Summary

The results of our evaluation of the AO H-R-R Pseudoisochromatic Plates may be stated briefly. This test agrees closely with the Prototype H-R-R test in its threefold purpose: (1) as a screening device to separate those with defective red-green vision from those with normal color vision; (2) as a device for the qualitative diagnosis of type of red-green anomaly (protan, deutan), and (3) as a device for the quantitative diagnosis of the anomaly (mild, medium, strong). As a screening test its results agree well with those of the AO Revised Selection. It can, therefore, be expected to detect in an unselected population close to 8% of males who from a practical point of view have a red-green deficiency.

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Marcus Gunn Phenomenon Following Squint and Ptosis Surgery

Definition and Review

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Marcus Gunn,[1] in 1883, published in the *Transactions of the Ophthalmological Society of the United Kingdom*, a case of "Congenital ptosis with peculiar associated movements of the affected lid." Earlier summaries of case reports were made by Sinclair,[2] in 1895 (32 cases) and Villard,[3] in 1925 (93 cases). Grant [4] reviewed the literature and published the 101st case in 1936. Falls, Kruse, and Cotterman [5] published a good summary in the *American Journal of Ophthalmology* in 1949. They collected 115 published cases. Spaeth,[6] in 1947, found 2 cases in 100 consecutive ptosis cases; to other authors this has appeared an unusually high incidence. Kanter,[7] in 1955, reports eight cases, of which six were typical.

The Marcus Gunn phenomenon is often referred to as the jaw-winking phenomenon. This is inaccurate, because it is not a wink but a lid retraction.

Clinical Picture

The typical case is a unilateral congenital ptosis in which there is a retraction of the lid on opening the jaw; this startling associated movement is usually obvious in infancy during sucking.

Some variations are reported: It is rarely bilateral (Marin Amat,[8] 1930). It rarely develops in later life due to trauma or spontaneously (unexplained) (Menacho [9]; Wilson [10]; Lagrange [11]). It may disappear temporarily (Ascher [12]). Ingraham and Campbell [13] produced the phenomenon by stimulation of the right parietal cortex while operating on a patient with Jacksonian epilepsy. Some inherited cases are reported (Falls, Kruse and Cotterman [5]). Some cases are associated with other deformities in addition to ptosis, e. g., paralysis of superior rectus (Lutz [14]), internal rectus or external ophthalmoplegia (Spaeth [6]), facial asymmetry (Alexander [15]), nystagmus (Soria [16]), or see-saw movements of the lids (Spaeth [6]). The case to be reported had a palsy of the superior rectus and some facial asymmetry associated with a unilateral congenital ptosis.

The stimulus to lid retraction has many variations reported:

A. Jaw
   1. Open (Kleinhans [17]; Menacho [9])
   2. Deviate—to opposite side gives upshoot
      —to same side gives increase in ptosis (Parsons [18]; Cooper [19])
   3. Protrusion (Falls, Kruse, and Cotterman [5])
   4. Closure (Rodger [20])
   5. Inspiration (Brain [21])

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6. Combinations of the above jaw movements, especially 1 and 2 (Sinclair [2]) or 1 and 4 (Spaeth [6])

B. Eye

1. Shutting sound eye (Fromaget and Brun [22]); Winkelman [23] describes a case in which the lid was elevated not only on closing the sound eye but also on staring with considerable effort into a mirror from a short distance
2. Depression of eyes (pseudo Graefe movement); may occur during recovery of oculomotor palsy
3. Elevation of eyes (Bielschowsky [24])
4. Side-to-side movement of eyes (Bielschowsky [24])
5. In facial paralysis (with both eyes depressed) attempted lid closure may lead to lid retraction
6. Cyclic oculomotor spasm.

Etiological Hypotheses

A. Abnormal Nervous Connections.—This hypothesis is favored by most authors, though they differ in opinion as to the locations of the aberration: (1) cortical or subcortical connections (Bing [25]; Walsh [26]; Lutz [14]; Kanter [7]); (2) internuclear connections (Walsh [26]) or faulty distribution in the posterior longitudinal bundle (Spaeth [6]); (3) infranuclear—some fibers of the third nerve

Fig. 1.—Appearance of patient before operations for ptosis.

Fig. 2.—One year after operations. Marcus Gunn phenomenon on jaw opening and jaw deviation.

may arise from the fifth nucleus (Dereux [27]; Marin Enciso [28]). More peripherally some fifth nerve fibers may reach the levator via the auriculo temporal nerve (Marin Amat,[29] 1924).

Confusion arises concerning the efferent path, because either striped or non-striped muscle is capable of lid elevation. Lewy, Groff, and Grant [30] postulate a proprioceptive arc whose afferent part is the mandibular division of the fifth nerve and whose efferent path is the autonomic fibers (questionably) via the ophthalmic division of the fifth nerve. This hypothesis led to the section of the motor root of the fifth nerve in one case, with equivocal results.

It seems strange that few cases of Marcus Gunn phenomenon are reported to be due to central nervous disorders, which might be expected to pervert connections occasionally. Ascher [12] reports a case during recovery from a unilateral third nerve palsy. After intensive antisyphilitic treatment, a lid, which had been ptosed for months, elevated involuntarily during chewing. The phenomenon disappeared when the patient became capable of voluntary lid elevation. Similar associated movements (pseudo von Graefe) have been attributed to syphilis and to pontine tumors and trauma.

B. Functional Interference.—Duke-Elder [31] considers a physiological explanation more acceptable. Three neurophysiological principles can be considered (Wartenberg,[32] 1946): (1) irritation of normally dormant connections, (2) release of inhibition (Ascher [12]), (3) spread of impulses by irradiation.

Fig. 3.—One year after operations. Cardinal positions.

C. Atavistic Reversion.—Harman [33] published this interesting theory in 1903. In fish there is a strong associated movement of jaw opening and eye opening—deep muscles contracting and superficial muscles relaxing. Thus a weak levator may only elevate the lid when the orbicularis is relaxed reflexly by jaw opening (deep muscle contraction). Supporting Evidence:

1. The Marcus Gunn phenomenon stimulated by inspiration (as reported by Brain [21]) suggests the primative gill, mouth, and eye opening reflexes in fish.

2. The corneomandibular reflex (jaw movement to opposite side when lid closure is stimulated by touching the cornea) is evidence of reflex connections between orbicularis and pterygoids (Wartenberg,[34] 1948).

3. Opening the mouth helps to open the eyes—especially in children—e. g., when instilling eye drops (Beaumont,[35]).

4. The reverse Marcus Gunn (reflex closure of lids on mastication during recovery from palsy of seventh nerve), or Marin Amat, syndrome. This is probably not a trigeminofacial movement but rather an interfacial movement (Wartenberg,[34] 1948).

This theory that the cause of the phenomenon is a release or irritation of an ancient phylogenetic reflex is supported by Ascher,[12] 1925; Brain,[21] 1933; Wartenberg,[34] 1948, among others—and appears the most likely theory to me.

Report of a Case

An attractive white woman aged 28, engaged in office work, requested an improvement in her appearance. A left ptosis had been present since birth associated with a down and out deviation of the left eye, whose vision had always

been defective. No jaw winking had been noticed in infancy or later. No other member of the family was affected.

On examination the left lid margin was approximately 4 mm. lower than that of the other side while the patient was looking ahead. The left lid elevated partly on upward gaze, and a lid fold was present. No Marcus Gunn phenomenon was noted. Left vision was fingers at 6 ft. There was some limitation of elevation in the left eye movements. The eye was divergent 15 degrees and depressed 15 degrees. Underaction of the superior rectus was marked, while the inferior rectus seemed overactive. No fusion was present. The left side of the face was smaller, and there was some asymmetry of the brow. Movie and still photographs did not reveal any jaw winking.

Surgery was performed in three stages. First left resection of internal rectus and tenotomy of external rectus. Second (three months later) resection of superior rectus and recession of inferior rectus. Third (two months later) shortening of levator tendon by Blaskowicz type of operation. Photographs taken between stages gave no hint of Marcus Gunn phenomenon.

The cosmetic result of the squint and ptosis surgery is good, but an obvious lid retraction is seen when the jaw is opened quickly. Deviation of the jaw to the opposite side produces slight retraction. The movement is best concealed by bending the head down and looking up, thus placing the lid in an elevated position so that further retraction is minimal and concealed by the eyebrows.

Comment

The patient is proficient at concealing the lid movements. Surgical correction of the Marcus Gunn phenomenon in this case does not seem to be warranted. Grant suggested cutting the motor root of the fifth nerve. Spaeth [36] advocates dissecting the entire levator from the tarsal plate and superior cul-de-sac, thus creating a complete paralytic ptosis. This paralytic ptosis is then corrected by use of the orbicularis and occipitofrontalis muscles.

With the etiological hypotheses in mind, the ptosis operation could not have caused abnormal nervous connections nor functional interference with reflexes nor the release of an atavistic reflex. The shortening of the levator tendon may make lid elevation slightly easier, but the lid retraction of the phenomenon is very vigorous. This makes it hard to believe that the levator could not have raised the lid when the lid was in a state of ptosis.

If the phenomenon was latent before the ptosis surgery, it was very well masked, because (1) there was no history of the phenomenon in infancy, (2) it was not seen by the orthoptist, (3) it was not noted by the surgeon, (4) it was not shown in numerous preoperative photographs or movies (especially as the pterygoid muscles were employed forcibly when the jaw was opened against the resistance of a chin rest during the movie).

Summary

A review of the literature on the Marcus Gunn phenomenon is presented, including a discussion of variations in the phenomenon and a summary of the various jaw stimuli causing the phenomenon. Other stimuli which may be effective in causing lid retraction are mentioned.

An examination of the etiological hypotheses is presented in an attempt to explain the reported case.

The case is presented of a young woman, with no history of jaw winking either in her family or herself as an infant, with a left complicated squint and left ptosis. Surgical correction was performed in three stages: first, horizontal recti; second, vertical recti; third, ptosis surgery. Photographs before and after each stage as well as adequate preoperative and orthoptic examinations failed to reveal any hint of the jaw-winking phenomenon until after ptosis surgery.

Medical Dental Bldg. (1).

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A Further Study of Streptococcus Vaccines in Nongranulomatous Uveitis

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In 1953 a report [1] was made on the diagnostic and therapeutic use of Streptococcus vaccines in nongranulomatous uveitis. In this paper the cutaneous reactions to the vaccines shown by 101 patients with nongranulomatous uveitis were compared with those observed in 107 patients with the granulomatous form of the disease. The incidence of foci of infection and the evidences of systemic granulomatous disease in the two groups were also determined. In addition, the results of desensitization therapy in 36 patients were reported. The important conclusions drawn from this study were as follows:

1. Patients with nongranulomatous uveitis show a high incidence of bacterial hypersensitivity (89%) as compared with patients with granulomatous uveitis (20%).
2. With occasional exceptions, this hypersensitivity was to one or more strains of streptococci, Subgroups A of the β-streptococci and the alpha group being the most important.
3. The intravenous administration of a specific Streptococcus vaccine in 36 patients with nongranulomatous uveitis gave a successful result in approximately 80% of such patients. This successful result was manifested by apparent desensitization of the hypersensitive patient and a remission of further attacks of ocular inflammation during the period the desensitized status was maintained.

Since the publication of this paper, 175 additional cases of uveitis have been tested for bacterial hypersensitivity and information is now available on the results of specific desensitization therapy in 50 additional cases. The purpose of this communication is to report the results of these diagnostic and therapeutic procedures in these patients.

Material Studied and Diagnostic Technique

Practically all of the patients here reported had been referred to the Wilmer Institute for study to determine, if possible, the cause of the uveitis. Ninety-seven of them had nongranulomatous uveitis, and seventy-eight had the granulomatous form of the disease. At the first ophthalmological examination the differential diagnosis between these two forms of uveitis was made in all the patients here included. Five patients in whom a differential diagnosis could not be definitely made are not included in this report. After the ophthalmological examina-

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tion the patients were all surveyed medically according to the regimen outlined elsewhere.[2] In addition to this medical survey, each patient was tested intracutaneously with a battery of stock Streptococcus vaccines. This consisted of 10 immunologically distinct alpha strains, all 42 of Subgroup A of the beta strains (Lancefield classification), 4 strains of Subgroup B, 1 strain each of the C and F subgroups, 1 strain of the γ-streptococci, and 1 strain of a Gonococcus. If any focus of infection was found in the teeth, nasopharynx, sinuses, tonsils, or genitourinary tract of patients with nongranulomatous uveitis, the bacterial flora of such a focus was determined by culturing the focus on broth and on blood agar plates. If any Streptococcus or Pseudomonas organisms were found, vaccines were prepared from them and the patient was tested with these for cutaneous hypersensitivity to his own autogenous organisms.

Results

A. The Diagnostic Use of Bacterial Vaccines

The results of the over-all studies for bacterial hypersensitivity in these 175 patients are shown in Table 1. There was an undue bacterial hypersensitivity in

TABLE 1.—*Bacterial Sensitivity in Uveitis*

Type of Uveitis	Cases, No.	Cases Hypersensitive		Cases Insensitive, No Bacterial Sensitivity	
		No.	%	No.	%
Nongranulomatous	97	79	82	18	18
Granulomatous	78	29	37	49	63

82% of the patients with nongranulomatous uveitis, in contrast to a 37% incidence of such sensitivity in the granulomatous group of patients.

In the nongranulomatous group there were 79 positive reactors to these vaccines. Sixty-two patients reacted only to strains of Subgroup A of the beta strains, while five patients reacted both to the Subgroup A strains and also to one or more alpha strains. Eight patients reacted both to stock streptococcal vaccines and to vaccines prepared from organisms recovered from their own foci of infection—seven to α-streptococci and one to an autogenous Pseudomonas organism. Three patients who did not react to any of the stock strains reacted to α-streptococci recovered from their own foci of infection, and one patient, to a Pseudo-

TABLE 2.—*Bacterial Sensitivity in Uveitis*

Type of Uveitis	Cases, No.	Specific Streptococcus Sensitivity			Other Organisms	Total Positive Reactions	
		Stock Vaccines Only	Autogenous and Stock	Autogenous Only		No.	%
Nongranulomatous	97	67	8	3	1 (Pseudomonas)	79	82
Granulomatous	78	29	0	0	0	29	37

TABLE 3.—*Bacterial Hypersensitivity in Uveitis*
(Studies I and II Combined)

Type of Uveitis	Patients, No.	Specific Bacterial Hypersensitivity				Total Positive Reactions		Total Negative Reactions	
		Stock Streptococcus Vaccines	Stock plus Autogenous Strains	Autogenous Streptococcus Vaccines Only	Other Organisms	No.	%	No.	%
Nongranulomatous	198	140	16	10	3	169	85	29	15
Granulomatous	185	50	0	0	0	50	27	135	73

monas organism. Thus there were 67 patients who reacted to stock vaccines only, 8 who reacted both to stock vaccines and to autogenous organisms, and 4 who reacted to autogenous organisms only. Of the 67 patients who reacted to stock vaccines, 5 were nonreactive to vaccines prepared from organisms isolated from their own foci of infection. There were 18 patients with nongranulomatous uveitis who did not react to any of the stock vaccines. These results are shown in Table 2.

When these results are combined with those reported in the previous communication, the over-all picture is an incidence of bacterial hypersensitivity in patients with nongranulomatous uveitis of 85% and in patients with granulomatous uveitis of 27%. Especially interesting is the finding that in the 169 reactors in the nongranulomatous group there were 10 persons who reacted to autogenous organisms recovered from their own foci of infection and did not react to any of the stock strains. It is also notable that when these patients were treated with vaccines prepared from the autogenous organisms they did well and showed a gratifying result of the treatment. The patients would have been classed as nonreactors and treatment would not have been instituted had reliance been placed entirely on the stock vaccines.

These reacting patients in the nongranulomatous group showed a tendency to multiple reactions to the various strains of Subgroup A of the β-streptococci. Thus 25 patients reacted to from 1 to 4 strains, 26 reacted to from 5 to 10 strains, 11 reacted to from 10 to 20 strains, and 5 reacted to over 20 strains. This same multiple reactivity was also found in the first series previously reported. When these two series are combined, 114 of the 156 patients who gave positive reactions to Subgroup A strains showed reactions to five or more strains. There were similar multiple reactions in the hypersensitive patients with granulomatous uveitis. This strongly suggests some common factor in the antigenic mosaic of these strains.

TABLE 4.—*Distribution of Reactions to Subgroup A of the Beta Strains*
(Studies I and II Combined)

Type of Uveitis	Total No. of Reactions	Reactions to 1-4 Strains	Reactions to 5-9 Strains	Reactions to 10+ Strains	Reactions to All Strains
Nongranulomatous	156	42	89	20	5
Granulomatous	50	24	18	8	0

These histories were also analyzed to determine the incidence of foci of infection and evidences of systemic disease in the two groups of uveitis. In the group of patients with nongranulomatous disease 45 (46%) showed evidences of active foci of infection and 16 (15%) had evidences of systemic granulomatous disease. In the group of patients with granulomatous uveitis 24 (31%) had foci of infection, while 55 (71%) had evidences of systemic granulomatous disease. When these figures are combined with similar figures from the first study, there are 187 patients in the nongranulomatous group, of whom 54% showed active foci of infection. In the granulomatous uveitis group the over-all incidence of foci of infection was 30%. In the patients with nongranulomatous uveitis the incidence of evidence of systemic granulomatous disease was 22%, while in the patients with granulomatous uveitis it was 74%. These figures are shown in Table 5.

While the incidence of foci of infection in the patients with nongranulomatous uveitis is almost double that found in the patients with granulomatous uveitis, it is doubtful if this is of significance. However, it is interesting that, when 47 patients in both series were tested with organisms isolated from their own foci of infection, 29 (62%) were hypersensitive to them, and in the patients specifically desensitized with autogenous vaccines this hypersensitivity appeared related to the uveitis. The greatly increased incidence of systemic granulomatous disease in patients with granulomatous uveitis is of course to be expected.

TABLE 5.—*Evidence of Foci of Infection and of Granulomatous Disease (Including Toxoplasmosis) in Granulomatous and Nongranulomatous Uveitis*

Type of Uveitis	Cases, No.	Active Foci of Infection Present		Evidence of Granulomatous Disease	
		No.	%	No.	%
Nongranulomatous	187	101	54	41	22
Granulomatous	185	55	30	137	74

B. The Therapeutic Use of Bacterial Vaccines

Streptococcus vaccines were prepared for 70 of the 79 patients with nongranulomatous uveitis in this series in whom a specific sensitivity to individual strains of streptococci had been demonstrated. These vaccines were composed of equal parts of the strains to which the patient showed the greatest sensitivity. When the patient showed reactions to autogenous strains recovered from his own focus of infection, this strain was likewise included in the therapeutic vaccine. As a rule, each vaccine contained from two to six strains. The vaccines were prepared and administered as outlined in the previous report. Three standard concentrations were prepared: No. 1 was a T-50 concentration of the organism as determined on the electrospectrophotometer. No. 2 was a 1:10 dilution of No. 1, and No. 3 was a 1:10 dilution of No. 2. The injections were given intravenously every four days. The usual initial dose was 0.1 cc. of No. 3. If the patient showed a reaction to this dose, still weaker dilutions, No. 4 (a 1:10 dilution of No. 3) or No. 5 (a 1:10 dilution of No. 4), were prepared. The essential point in treatment was to keep the dose below the patient's point of reactivity and to avoid both systemic and focal reactions. If there were no reactions to the first

dose, it was gradually increased (0.1 cc. at each injection) as the antibody appetite of tissues gradually became satisfied. The dose of 0.5 cc. of the No. 1 dilution was considered the maintenance dose. When this point was reached, it was continued for six months at weekly intervals.

Twenty of the seventy patients for whom vaccines have been prepared have either been lost or have been treated for such a short time that the results of the therapy cannot be evaluated. There remain 50 patients in whom there is reasonably reliable information, obtained either by reexamination of the patient or by report from the referring physician. Twenty-seven of these patients can be classed as successes. The attacks of uveitis have ceased, and there have been no recurrences as long as the desensitized status has been maintained. Thirteen patients can reasonably be classed as "improved." These patients were never completely desensitized. However, after prolonged treatment (one year or more) the interval between the attacks has lengthened beyond any previous remissions the patient may have enjoyed and the intensity of any attacks has been greatly lessened. Nineteen patients are classed as "failures." Sixteen of these patients have completed their course of desensitization, but they continue to have attacks of iritis of the same intensity and at the same intervals as before treatment. In these 16 patients the hypersensitivity demonstrated by the diagnostic tests was probably not related to the etiology of the uveitis. Three other patients discontinued treatment in the early stages because of transient, but sharp, focal reactions in the eye coming on 24 to 36 hours after the injections of the vaccine. These reactions did no harm, but they persisted even though the dose of the vaccine was reduced. Although the occurrence of these focal reactions supported the cause-and-effect relationship between the hypersensitivity and the uveitis, nevertheless, since the patients could not take the treatment, they are classed as failures. These results, as well as those reported in the previous paper, are summarized in Table 6. In a total of 86 patients who have been treated, the results of therapy have been successful in 54, or 63%. Thirteen others (15%) are definitely improved, while in nineteen (22%) the treatment has been a failure.

TABLE 6.—*Results of Desensitization with Specific Streptococcus Vaccines*

	Cases, No.	Period of Post-Treatment Observation	Successes	Improved	Failures
First series	36	3-12 yr.	27	3	6
Second series	50	6 mo.-3 yr.	27	10	13*
Totals	86		54† (63%)	13 (15%)	19 (22%)

*Three patients abandoned treatment because of focal attacks after small doses of vaccines.
†In 10 cases recurrences after cessation of treatment were synchronous with return of sensitivity.

In 10 of the patients classed as successes there have been recurrences. At the completion of treatment they were free of all ocular inflammation and, when tested for hypersensitivity, were found to be completely desensitized. At periods ranging from three months to several years after cessation of treatment, there was a recurrence of the iritis. When the patients were retested with the diagnostic vaccines it was found there had been a recurrence of the bacterial hyper-

sensitivity. This recurrence of sensitivity had either preceded the ocular reaction or was synchronous with it. When these patients were again treated they were once more desensitized, with an accompanying remission of the attacks.

Comment

The experiences of the last three years with the diagnostic and therapeutic use of Streptococcus vaccines in nongranulomatous uveitis confirm those previously reported. There is a high incidence of streptococcal hypersensitivity in the disease, and desensitization therapy has, in the main, been successful. There are several pitfalls, however, which must be emphasized.

Primarily, when a specific bacterial hypersensitivity has been demonstrated there is no way of stating definitely that it is etiologically related to the uveitis. It may only be the residuum of a previous streptococcal infection and be quite unrelated to the ocular inflammation. If there are focal reactions in the eye following the therapeutic administration of the vaccine, this is excellent evidence of a cause-and-effect relationship. If there are repeated systemic reactions and no change in the eye, this may equally well be construed as evidence that the hypersensitivity and the ocular inflammation are unrelated. Probably the best evidence for a cause-and-effect relationship is the therapeutic result—a subsidence of all inflammation and cessation of the attacks synchronous with desensitization.

Patients may react in different ways to the administration of the vaccine. Many take it without reactions, achieve the desensitized status in from six to nine months, and thereafter remain desensitized and free of attacks. In other patients the hypersensitivity returns after cessation of treatment, and with it there is often an ocular relapse. These patients require maintenance doses to prevent those recurrences. There are two patients who appear almost wedded to the vaccine. They stay free of attacks as long as they keep up the injections, but they have recurrences a few months after stopping treatment.

The over-all figure of 78% either successes or improved is even more impressive when one considers the class of patients treated. These were all patients who had suffered recurrent attacks and usually had badly damaged eyes. While treatment with the corticosteroids might help somewhat, it could not in itself control the inflammation. In these bad cases with a gloomy prognosis, this desensitization therapy appeared to offer the only real hope of controlling and preventing the ocular disease. It is somewhat heroic treatment, trying to both the patient and the doctor. Properly given, it appears free of danger—at least no severe or alarming untoward reactions have as yet been observed. It is certainly not to be recommended for the light case where the attacks may be years apart and which can be controlled by the adrenal corticosteroids. It should be reserved for severe cases, for patients in whom the attacks are either frequently repeated or in whom the inflammation is chronic. In these patients, when the attacks of nongranulomatous uveitis actually threaten vision and the functional integrity of the eye, especially if the inflammation does not respond to conventional steroid therapy, specific desensitization offers a reasonable and probably the only chance of controlling and preventing the recurrent attacks.

Conclusions

1. There is a high incidence of hypersensitivity to various strains of streptococci in patients with nongranulomatous uveitis.

2. This hypersensitivity may be either to stock strains of immunologically distinct streptococci or to streptococci isolated from a focus of infection in the patient.

3. Desensitization of the hypersensitive patient with the specific organism to which the hypersensitivity has been demonstrated has given a successful result in a large percentage of patients thus treated.

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Total Ascorbic Acid in Aqueous Humor and Serum in Indian Patients With and Without Cataract

Its Physiologic Significance

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The total ascorbic acid concentration in aqueous comprising two components, the reduced form as *l*-ascorbic acid, and the oxidised product, as dehydro *l*-ascorbic acid,[3] although very variable, is very much higher than in blood plasma. In various animals, including man, the concentration ratio approximates 6-8:1.* Moreover, recently, it has been found that the concentration of ascorbic acid in the aqueous humor varies approximately as the concentration in the serum, regardless of whether or not the lens is cataractous, the subjects of this investigation being normal patients, aphakic patients, and patients whose lenses were sufficiently opaque to warrant extraction.[7] The present paper deals with a comparative study of total ascorbic acid in aqueous and serum of Indian patients of three categories: (*a*) with normal lens, (*b*) with different types of cataract, (*c*) with lenses extracted previously.

Selection of Patients

The selected subjects were first subjected to a thorough examination with a Zeiss-Opton slit lamp with dilated pupils to ascertain the condition of their lenses. The following types of patients were selected:

	Cases, No.
(1) Different types of cataract	8
(2) Aphakias	2
(3) Aphakias with onset of phthisis bulbi due to postoperative endophthalmitis	1
(4) Normal lenses	2

(1) *Different Types of Cataract.*—(*a*) Cupuliform Cataract (2 Cases): This type, also known as posterior saucer-shaped cataract of Vogt (1919),[2] showed lenticular opacities in the posterior layers of the cortex immediately underneath the capsule. There was associated lenticular sclerosis to a minor degree, but the rest of the lens fibers were clear.

(*b*) Early Nuclear Cataract with Onset of Cupuliform Cataract (2 Cases): There was an increase in optical density of the nucleus to such an extent that vision was impaired. There was no opacity of the lens fibers except at the site of onset of the cupuliform cataract.

(*c*) Mature Cuneiform Cataract (2 Cases): The lens was totally opaque and

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* References 5 and 6.

white, but still the spoke-like arrangement of cortical opacities, characteristic of cunexiform cataract, could be identified.

(*d*) Hypermature Cuneiform Cataract with Sclerotic Change (1 Case): The lens was totally opaque; the capsule was thickened, appeared yellowish, and showed deposits of calcium. The whole lens on intracapsular extraction was found to be shrunken and flat.

(*e*) Fuchs' Heterochromic Cyclitis[4] with Total Cataract (1 Case): The iris appeared depigmented, with the architecture of the trabeculae lost. There were no posterior synechia but plenty of fine nonpigmented keratic precipitates. The lens showed a total diffuse opacification.

(2) *Aphakia* (2 Cases).—Only in both the cases, there was a very thin after cataract. In one the lens was removed one year ago and in the other one month ago.

(3) *Phthisis Bulbi* (1 Case).—The lens was extracted two years ago, and endophthalmitis followed. The eye quieted but the tension became subnormal and light perception was lost. The cornea was clear, wthout any keratic precipitates, but it was smaller than normal. The anterior chamber was present, but the pupil was completely occluded by an exudative membrane.

(4) *Normal Lens* (2 Cases).—The lens was clear in both cases. In one, optical iridectomy was done for a central corneal opacity. In the other, the eye was perfectly normal, the fellow eye being operated on for traumatic cataract.

Method

Following antibiotic treatment for 48 hours in the form of crystalline penicillin drops, 2500 units per cc. every 2 hours, and oxytetracycline (Terramycin) with polymyxin B ointment twice daily, in all the cases aqueous was collected under local drop anesthesia in the form of 4% cocaine hydrochloride, except in the case of a child, when a general anesthetic was used. With proper aseptic precautions, a No. 18 British-made hypodermic needle fitted to a dry tuberculin syringe, graduated in 1000th parts of a cubic centimeter, was pushed through the lower part of the cornea near the limbus, taking due care not to injure the lens. The aqueous was aspirated very slowly until the anterior chamber was almost completely abolished. The amount of fluid drawn was ascertained at once and was transferred to a round-bottomed centrifuge tube, 15×105 mm., the thickness of the wall being 0.5 mm. The amount of aqueous collected varied in different cases as follows:

	Amount of Aqueous, Cc.
Mature cuneiform cataract (anterior chamber slightly shallow)	0.15
Phthisis bulbi	0.1
Normal lens in a child	0.25
Others	0.2

Concurrently with the collection of aqueous, about 7 cc. of blood was collected from the anterior cubital vein in each case for the analysis of the ascorbic acid content in the serum.

It was noticed that the anterior chamber was reformed in each case within 5 to 10 minutes of the aspiration, except in the case of phthisis bulbi, when a much longer time was required. The intraocular tension remained very low, so that an intraocular operation could not be undertaken at the same sitting.

Analysis

The ascorbic acid in the aqueous humor was determined by the method of Roe and Kuether,[8] with certain modifications.

In the present series of experiments, the whole quantity of aqueous humor collected in the centrifuge tube was mixed with 4% trichloroacetic acid and made up to a volume of 4 cc. After the mixture was kept at 30 C for five minutes, it was centrifuged. From the supernatant fluid a 2 cc. aliquot was taken in a test tube and bromine was added to the tube in very small quantities at a time, with shaking, until a yellow color was obtained. The excess of bromine was then driven off by passing air through the solution. By this treatment the whole of the ascorbic acid was converted into the dehydro form. One cubic centimeter of dinitrophenylhydrazinethiourea reagent was added to the solution. The mixture was incubated at 37 C for three and one-half hours. It was then cooled by immersing the tube in ice. One cubic centimeter of 85% sulfuric acid was added cautiously to avoid any rise of temperature. The mixture was shaken and kept at 30 C for one-half hour. The color developed was read in a Klett-Summerson photoelectric colorimeter (Model 900-3) with filter 540 mμ and compared with a standard solution of ascorbic acid which was prepared in the same concentration as that of the aqueous humor. This had to be found out by trial. The colorimeter was, however, initially set at zero with a blank having the following composition:

4% Trichloroacetic acid	2 cc.
2,4-Dinitrophenylhydrazine-thiourea reagent	1 cc.
85% Sulphuric acid	1 cc.

2,4-dinitrophenylhydrazine	2 gm.
Thiourea	4 gm.
Sulfuric acid (9N)	100 cc.

Ascorbic acid in serum was estimated according to the same method as described above, with the only difference that 1 cc. of serum was mxied with 3 cc. 4% trichloroacetic acid. Other operations were exactly similar to those for aqueous humor.

Results

Concentrations of ascorbic acid in the aqueous humor and serum in different eye conditions are shown in the Table.

Concentration of Ascorbic Acid in Aqueous and Serum

Case	Age, Yr.	Eye Condition	Total Ascorbic Acid, Mg./100 Cc. Aqueous Humour	Serum	Ratio Aq.H./Serum
1	65	Cupuliform cataract	4.0	0.8	5.0
2	72	Cupuliform cataract	3.33	0.8	4.1
3	60	Early nuclear cataract	5.92	1.37	4.5
4	55	Early nuclear cateract	4.44	1.37	3.2
5	59	Mature cuneiform cataract	5.10	1.42	3.5
6	40	Mature cuneiform cataract	4.26	1.24	3.4
7	71	Hypermature cuneiform cataract with sclerotic change	7.90	1.88	4.2
8	26	Fuchs' heterochromic cyclitis with total cataract	5.50	1.55	3.5
		Cataractous lens, Av.	5.05	1.30	3.9
9	60	Aphakia	4.57	0.8	5.7
10	50	Aphakia	5.19	1.42	3.6
		Aphakia, av.	4.88	1.11	4.6
11	71	Phthisis bulbi	14.8	1.88	7.8
12	28	Normal lens	3.58	1.34	2.6
13	12	Normal lens	3.20	2.40	1.3
		Normal lens, av.	3.29	1.87	1.9

The results show that there were not very wide variations in the concentration of ascorbic acid in aqueous humor and serum among the various patients examined. The ratio of ascorbic acid content in aqueous to that in serum was more or less the same in persons with cataractous lens or with aphakia, although the ascorbic acid content in the aqueous increased with that of the serum. The ratio in patients with normal lenses was rather low, but that in the patient with phthisis bulbi was definitely higher.

Comment

The analysis of the total ascorbic acid content shows in general that the concentration of this substance is always higher in aqueous than in serum, although the present findings were of a much lower denomination than those of previous observers.[7] There are three possible explanations for the higher concentration of ascorbic acid in aqueous humor[1]: 1. There is direct synthesis of the ascorbic acid by the lens. 2. The ascorbic acid enters the eye from the blood in the oxidised form and this is reduced by the lens. The blood-aqueous barrier is presumed to be relatively impermeable to the reduced form, which therefore cannot escape sufficiently rapidly from the eye to prevent accumulation in the aqueous humor. 3. There is secretion of ascorbic acid by the ciliary epithelium. If the lens is responsible for the higher concentration of ascorbic acid in aqueous it must produce it through some metabolic process characteristic of itself. But the results reported in the Table show that both in cases of total cataract, where the metabolism of the lens was completely stopped, as also in cases of very early cataract with a large number of lens fibers still remaining transparent, where there was every likelihood that the metabolism was still going on, the concentration of ascorbic acid was higher in aqueous and approximately at the same level in the two conditions. Moreover, in cases of aphakia, also, where there was practically very few lens fibers left, the result was similar. These findings corroborate the conclusions of previous observers like Purcell and others[7] and are strong evidence against the theory that the lens is responsible for maintaining a higher concentration of ascorbic acid in aqueous humor.

The role played by the ciliary epithelium in maintaining the higher concentration of ascorbic acid in aqueous is not yet definitely known. On analysing the results, one very striking feature becomes evident. The ratio of ascorbic acid in aqueous to that in serum in the patients with cataractous lenses is approximately only 4:1, whereas the same finding by Purcell and others[7] was approximately 19:1, although the ascorbic acid content was expressed in milligrams per 100 cc. of fluid in the present series, whereas the same was calculated as milligrams per 100 gm. of fluid by the previous observers.[7] As evident from the table, the low ratio figure is due to the lower ascorbic acid content in aqueous. The present study was carried out in patients who were all colored people, with a high pigment content in the ciliary epithelium. If the ciliary epithelium is at all responsible for the formation of the ascorbic acid in aqueous, is it possible that the higher pigment content exerted a retarding effect on this process, so as to explain the uniformly low ratio of ascorbic acid content in the present analysis? There is only one bit of evidence, although very meager, which is in favor of this theory. In the case with phthisis bulbi without a lens, the ratio was almost double. As there was still an anterior chamber and aqueous could be withdrawn, a part of the ciliary body was undoubtedly still functioning, but perhaps the pigment-containing epithelium, being the deeper layer, was more

seriously damaged, thus losing its retarding effect upon the formation of ascorbic acid and explaining the higher ascorbic acid content of the aqueous. On the other hand, in the case showing Fuchs' heterochromic cyclitis, where the process of cyclitis was a very mild and insidious, the retarding effect of the pigment epithelium was intact and the ratio of ascorbic acid was on the same level as in other cases. The very low value of ascorbic acid ratio in the two cases with normal lenses is remarkable, but we cannot suggest any possible explanation for this.

Summary and Conclusions

The relationship of the ascorbic acid content in aqueous to that in serum was approximately the same in patients with various types of cataract and with aphakia; thus evidently the lens had no influence in maintaining that relationship.

The ascorbic acid content in aqueous, although varying approximately with that in serum, was rather low in the present series. An explanation related to the function of the ciliary epithelium is suggested.

The eyes with normal lenses showed a very low content of ascorbic acid in aqueous. The reason for this discrepancy is not understood.

Lt. Col. N. C. Chatterjee, Surgeon-Superintendent, gave permission for the publication of this paper.

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Refractive Changes in Normal Young Men

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It has been known for some time that refractive changes occur during adolescence and early adult life, just as they do in childhood and puberty. Although most physiologists consider these to be associated with the continuing growth process, there is a minority group which links such changes to other causes. Genetic contributions, racial predisposition, nutritional influences, convergence effects, and the excessive use of the eyes for close work have all been advanced as possible explanations for the changes in refraction that develop in healthy young people after the period of rapid growth has passed. With the exception of those cases where visual deficiency is due to pathology, the problem is ordinarily not of major importance and is easily corrected by the prescription and use of glasses.

Consideration of the refractive changes in young people has received only occasional attention in the past.* However, there has been a transition in our society during the last 15 years from one which was essentially civilian to one in which all physically qualified young men are obligated to do military service, and the fact that many components of military activity have fairly rigid standards for ocular efficiency has made it necessary that more consideration be given to the refractive changes that occur in late adolescence.

It has been found troublesome that many adolescents who meet prescribed visual standards at the beginning of their training are not visually qualified at the completion of their course to accept the responsibilities for which they have been trained. Others must be removed from highly technical specialties because their visual acuity has fallen below required standards. The naval and military academies, the Reserve Officer Training programs in colleges, aviation and submarine-training schools, Officer Training programs in colleges, aviation and submarine training establishments have become acutely aware of the necessity for selecting only the candidates whose vision can be expected to continue to meet required standards after graduation.

In order to resolve this problem, various visual standards have been reassessed, and adjusted where possible, so that the visual demands of a specific military job and the availability of young men to do the job can be brought into a more realistic balance.

For the military ophthalmologist the problem of refractive changes in young

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The opinions or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the view of the Navy Department or the Naval Service at large.

* References 1-3.

men has, therefore, become considerably greater than it is for his civilian colleague, and the purpose of this paper is to present observations and conclusions that can be applied when selecting candidates who must maintain a relatively high visual acuity to continue in certain military categories. Since many candidates consult civilian eye specialists in regard to borderline visual acuity, it is felt that this subject is of general interest.

In 1949 the Department of Ophthalmology at the U. S. Naval Academy, Annapolis, Md., was asked to determine the reason for the relatively high attrition of midshipmen because of deterioration of visual efficiency, when these same men had been admitted to the Academy as visually qualified. The problem was not a new one and had been previously investigated at the academy. Corrective measures had been undertaken to improve illumination and diet, as well as to select textbooks with proper size print and reflectance of paper. Firm adherence to the visional requirements for admission was demanded. After these factors were brought close to optimum, it was decided to study the ophthalmic records of four consecutive classes, three of which were then at the Academy.

A brief explanation of the visual requirements for admission to the Naval Academy should be given. It is required that an applicant have visual acuity of 20/20 and be able to read correctly 17 of the prescribed 20 Pseudo-Isochromatic Plates (A. O. 1941) or pass the Farnsworth Color Vision Lantern, and that he be free of disease of the eyes and adnexa. A history of diplopia or asthenopia is disqualifying, as is a cosmetically disfiguring strabismus at the time of the examination. No limits were set for phorias or fusional amplitudes, and there was no requirement for stereopsis. At the present time third-degree fusion is required.

During the physical examination for admission each candidate was tested for visual acuity on a 20 ft. lane, using both Snellen and nonserif test letters. The walls of the lanes were painted with a prescribed "flat Navy #9 Pearl Gray" paint, with 46% reflectivity; ceilings were white, with 75% reflectivity. Illumination of the walls approximated 4 foot-lamberts-(f.-L.) and the target brightness was adjusted to 15 f.-L. Light struck the target area at an angle of 45 degrees from above, and all luminaries were so shaded that no light glared into the applicant's eyes. The structure of the lanes was such as to make them shadow-free. each applicant was tested individually, and squinting, excessive winking, "stretching," "butterflying," or other aids to naked vision were not permitted. Care was taken to determine the best performance for each eye, and the requirement was to read a line of at least eight 20/20 test letters forward or backward as directed. When two test lettrs were called incorrectly, charts were changed so that test letters of different construction were used, and the applicant was rejected if his visual acuity was 20/20−2 or more.

Following examination for color vision, cycloplegia was induced with 4% homatropine hydrobromide solution, using 1 drop in each eye every five minutes for four applications. Retinoscopy was performed one hour later, and both retinoscopic finding and the cycloplegic acceptance were recorded. Random checking of residual accommodation was used as a means of controlling the level of cycloplegia within a group, and further use of homatropine solution was made whenever needed. Ophthalmoscopic examination was done through the dilated pupil. An ophthalmic record was opened showing the results of the initial examination and was maintained until the midshipman graduated. Each year, as part of the annual physical examination, unaided visual acuity was posted on this record, and, if the

acuity fell below 20/40, cycloplegic examination was again done and recorded. Any interim injuries, infections of the eyes or adnexa, and any ocular complaints were entered, as were all prescriptions for corrective lenses. The fourth annual physical examination given was to determine qualification for commission as an ensign in the U. S. Navy or a second lieutenant in the U. S. Air Force. At this time cycloplegic refraction was required for all men who were otherwise qualified for aviation training, and was also used for any man who had less than 20/40 visual acuity. At graduation each ophthalmic record had at least five entries and contained sufficient material to permit an over-all evaluation of the four-year ocular history of each individual. This chronologic tabulation shows at what age visual acuity started to diminish and the nature of its subsequent progress through each scholastic year. If the visual acuity fell below 20/100 in either eye, the midshipman was separated from the Academy.

It must be recalled, in the evaluation of the figures that will be given, that young men at the service academies lead lives so regimented for economy of time that each spends about the same amount of time in classroom, laboratory, study, exercise, sleep, and recreation. The diet, carefully planned by dietitians, is the same for all and is generous. At the Naval Academy the living environment is essentially the same for all men, and the factors of illumination and light reflectance have been carefully engineered to provide proper study conditions. The level of personal and group hygiene is very high, and is so maintained by regulation and by daily inspection. It therefore seems reasonable to conclude that the 3700 midshipmen composing this study group led lives so essentially similar that whatever nontraumatic external factor might affect the eyes or refractive status of any one would exert a similar influence on the eyes of all.

This group must be considered to be highly selected, for midshipmen are carefully screened physically, psychologically, and academically. Since they are a selected group of normal, healthy, intelligent adolescents, their further physiologic development might well be considered the normal biologic expectancy in a controlled environment. Private correspondence with departments of student health at two American universities which had reviewed the physical status of their male student body to determine the probable loss of men through required military training indicated that the general level of physical competence and visual acuity was initially higher and remained higher in our selected midshipmen group than in the physically unselected student bodies of the two universities. In spite of the propitious influences derived from careful selection and a controlled environment, the development of some degree of visual impairment was about 18% in each class. The cause of decreased acuity was almost exclusively myopia or some form of myopic astigmatism.

In reviewing the records, it was observed that myopic corrections were prescribed for many men during their first year and that these were rather regularly increased in strength up to the time of graduation. As the wearing of glasses by officers has been traditionally considered nonmilitary, glasses were prescribed carefully, and only when really needed by the midshipmen. It was also noted that, of those needing glasses, most showed essentially emmetropic refraction on admission and that more glasses were issued to younger men than to the older ones .

It was therefore decided to separate the records of two classes (1949 and 1950) according to their age and cycloplegic acceptance on admission to the Naval Academy, and to determine the incidence of visual defects within these groups. As the

examinations of these classes had been made by several examiners, a gross division appeared indicated in the weighing of initial cycloplegic findings. As the astigmatic components were relatively small, the use of spherical equivalents seemed a justified and convenient method of expressing refractive errors. A spherical equivalent of ½ D. of plus sphere was selected for its apparent probability of significance, and those men who showed this or less on their admission cycloplegic refraction were divided according to their age at time of admission. The 17- and 18-year-old group was computed as a single division; the 19- 20- and 21-year-olds each constituted a separate division.

When this arrangement of the data was completed, it was found that 624 of the 660 records of visual defect had been classified; only 36 examples of developing visual defect had occurred in the 1419 men who had a spherical equivalent greater than ½ D. of plus sphere on admission, regardless of age. In the group of 624 admissions whose initial cycloplegic refraction was ½ D. or less of plus spherical equivalent, the distribution of defects occurred as follows:

Of 117 admissions in the 17- 18-year age group, 91, or 77%, developed myopic defects; of 261 admissions in the 19-year age group, 116, or 44.4%, became defective; of 172 admissions in the 20-year age group, 66, or 39%, showed loss of vision; of 74 admissions in the 21-year age group, 11, or 14.8%, became myopic in some degree.

This method of dividing the visual failures into age groups according to their cycloplegic findings on admission makes it appear that the younger the applicant, and the more emmetropic he is, the greater the likelihood of his developing some type of myopic refractive error.

It must be pointed out that there were a few in the category showing less than ½ D. of plus spherical equivalent who showed a minus spherical equivalent and were indeed technical myopes on admission. The requirement of 20/20 vision made these cases a small minority, and in only four cases was a spherical equivalent of −½ D. sphere found. The subtraction of these few from the total makes no appreciable difference in the relative percentages of failure, and because the problem presently revolves around the concept of "20/20 vision" as a standard, it is only fair to include them in the figures.

It must also be noted that with each year of advance in age the percentage of failures among the essential emmetropes decreases, so that at age 21 only 14% of defectives are noted. It would appear that the 20/20 acuity requirement eliminates many from this 21-year-old group who might have been eligible four years earlier.

Following this exploratory investigation, it was considered desirable to analyze the class of 1952 somewhat more carefully, as this class had been admitted and followed during their four-year course by one ophthalmologist. The data on this class were more detailed and promised greater consistency. The same age divisions were retained, but the classification of cycloplegic acceptance was subdivided to show those admissions who had ½ D. of plus spherical equivalent or less; those

Candidates Qualified for Aviation (20/20 Vision)

	Spherical Equivalents		
	+1.00 D	+0.50 - +1.00 D	+0.50 D
Class of 1952 in 1948	138	94	12
Class of 1952 in 1952	46	112	86

whose spherical equivalent fell between +½ and +1 D., and those whose initial refraction exceeded +1 D.

Figure 1 shows a bar graph representation of these findings with the figures upon which the percentages were calculated. This presentation again demonstrates the tendency of younger emmetropes to fail, the reduced incidence of visual defect as age advances, and the markedly fewer failures in those with initial acceptances above ½ D. of convex sphere.

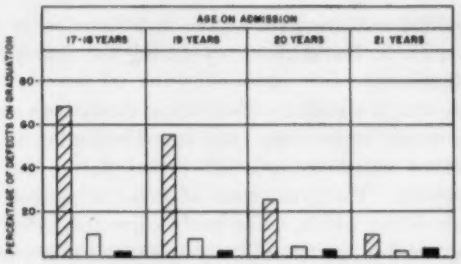

Fig. 1.—Percentage of graduates with defective vision, class of 1952. Hatched areas represent +0.50 D. spherical equivalent or less on initial cycloplegic refraction; size of groups 169, 110, 94, 153. Clear areas, +0.50 to +1.00 D. spherical equivalent; size of groups 56, 54, 50, 65. Black areas +1.00 D. and above spherical equivalent; size of groups 119, 61, 32, 64.

Analysis of the four classes gave essentially the same results as those depicted in Figure 1, and the classes show high correlation with each other. No significant difference exists between the age groups of any one class as compared with similar age groups in other classes studied when such comparisons were made on the basis of being above or below the +½ D. spherical equivalent level.

Figure 2 represents four classes, totaling 3969 midshipmen, presented on the single consideration of whether or not their initial cycloplegic acceptance exceeded the spherical equivalent of ½ D. of plus sphere.

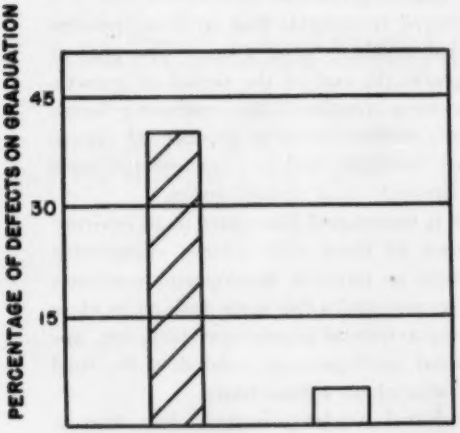

Fig. 2.—Defective vision for four years, 3969 men. The hatched areas represent spherical equivalent +0.50 D. or below; clear areas, spherical equivalent exceeding +0.50 D. (cycloplegic acceptance on admission examination).

To be physically qualified for assignment to aviation training following graduation from the Naval Academy, a candidate must have, among other ocular requirements, 20/20 visual acuity, no evidence of myopia, not more than 2.50 D. of hyperopia, and not more than 0.75 D. of cylindrical correction when examined under cycloplegia.

The Table relates 244 members of the class of 1952 who were found physically qualified for aviation training, according to the strength of cycloplegic equivalent upon admission and upon graduation. A very definite shift in the direction of decreased hypermetropia is evident. In this group the average loss of ability to accept plus sphere under cycloplegia was 0.375 D., while the median in the group fell just above ⅛ D.

Summary

Material is presented indicating the nature and direction of refractive changes in young men at the U. S. Naval Academy during the four-year period between admission and graduation.

The data indicate that a significant correlation exists between the younger age group who are essentially emmetropic, and the distribution of refractive errors expressed in diminished visual acuity which occurs during the four years of attendance at the Academy. The great mass of these refractive errors consists of some form of myopic defect which, while easily corrected, interferes with the free selection of, or assignment to, certain military specialties that require high levels of visual efficiency; moreover, these errors also disqualify many midshipmen from being commissioned in the unrestricted line for which they have been trained.

Analysis of the records of several classes repeats the pattern so consistently that tables of anticipation can easily be constructed to aid in the selection of candidates or to prepare for their eventual disposition.

A definite shift away from hypermetropia toward emmetropia or myopia occurs between the ages of 17 and 22. This shift appears to be constant in those who do not develop disqualifying visual defects, as well as in those who do.

Comment

The mechanism by which the many variable components of normal vision are arranged during the twenty-odd years of human growth is so complex that it is little understood. It has often been considered remarkable that so many persons attain the happy equipoise of variables that produces good vision. The goal of nature appears to be refractive emmetropia at the end of the period of growth. If that goal is reached before growth has been completed, the continuing forces of development continue to rearrange the variables so as to produce an optical system that is overly strong in its refractive functions, and as a consequence some type of myopic defect is produced which prevents clear distant vision.

In rather carefully selected group which is maintained four years in an environment of near-optimal hygiene, the tendency of those who achieve emmetropia early in their adolescence to become myopic as physical development continues is striking. As the same pattern unfolds in essentially the same fashion in class after class, it is difficult not to accept it as a normal physiologic evolution, apparently based upon a genetically determined predisposition, related to the final growth increment, and predictable when evaluated on a mass basis.

The incidence of these defects at the Naval Academy is much less than in the general population,† less than among unselected student bodies of similar age,‡ and less than among illiterate aborigines of certain parts of the world.[6] In view of this, it is not justifiable to indict any influence peculiar to the way of life, the

† References 3 and 5.

‡ References 3 and 4.

curriculum, or the environment of the Naval Academy as etiologic to the failures described. It does seem justifiable to consider this refractive myopia as the normal pattern of development in the final trimester of human growth. (See also report of Hayden and Goff.[7])

Conclusions

1. Seventeen- and eighteen-year-old adolescents who have 20/20 vision, and whose cycloplegic acceptance is ½ D. or less of plus spherical equivalent, are likely to develop some degree of myopic-type refractive error and diminished visual acuity during the next four years of their life.

2. This process, which has been described with somewhat greater incidence of visual disability in the general population, occurs in carefully selected, normal, healthy young men who are maintained in an environment that is engineered toward ideal hygiene. It may therefore be considered a concomitant of normal physiologic development and predictable under such circumstances as have been described.

3. As adolescence recedes, the relation of age to emmetropic refraction becomes less significant in the anticipation of later diminished visual acuity, so that at age 21 men with 20/20 acuity and an essentially emmetropic refraction have greater than 90% likelihood of continued normal vision.

4. If all adolescent candidates for training in military and civilian specialties where continued 20/20 acuity is necessary were required to have a cycloplegic acceptance in excess of ½ D. of plus spherical equivalent, the attrition from refractive myopia would be less than 10%.

U. S. Naval Hospital.

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Annual Reviews

NEURO-OPHTHALMOLOGY

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THIS REVIEW of neuro-ophthalmology attempts to assemble in abstract form the reported and published literature of the 12-month period ending July, 1956. Where it was necessary to rely upon current abstracts, because the original foreign articles were not available, the date of publication may be a few months earlier. It is impossible to cover the entire subject on a world-wide basis, but access to 33 relevant journals and several new books furnished considerable information, from which this material is assembled.

It is my endeavor to continue the last review of this subject by Payne [1] and to integrate the subject with the recent review of the optic nerve by Wagener.[2] The optic nerve will be considered only when it is implicated by intracranial affections.

The Visual System

Grouping and sequence are rather difficult. It is thought best to mention the reports of the visual system according to structure. However, considerable study has been currently presented on the blood supply and vascular conditions involving the visual system, and so this subject will be reported separately.

The Optic Nerve

An interesting demonstration of the histoanatomy of the optic nerve is given by Wolter,[3] in which the effect upon the cells of various pathologic processes is described.

A symposium of diseases of the optic nerve by Carroll, Henderson, Zimmerman, Rucker, and Walsh [4] contains much information regarding the present knowledge of optic nerve affection. Zimmerman also includes discussion of intracranial conditions at higher levels.

Chamlin [5] presents a study of differential diagnosis of optic neuritis. He states that the most important conditions simulating retrobulbar neuritis are mass lesions compressing the optic nerve and chiasm. An article on the production of retrobulbar neuritis as a complication of infectious mononucleosis is presented by Shechter, Lipsius, and Rasansky.[6] Böke [7] describes neuritic changes in the optic nerve in tuberculous meningitis caused, as he states, from tubercles in the nerve from tuberculous endangiitis. Nonnenmacher [8] reports upon optic neuritis in lactation. Calcium studies, a very important factor, are not described in the article as abstracted. Observations of the course of treated syphilitic primary optic atrophy are presented by Hahn, Zellmann, Naquin, Cross, and Marcus.[9] In a study of 141 patients the progress was found to continue in one-third of the cases during the first year, one-half by the second and third years, and three-fourths by the fourth and fifth years.

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Toxic Affections

Although toxic affections may implicate the intraorbital optic nerve and retina not infrequently, there is general or diffuse cerebral involvement, with symptoms from higher visual or oculogyric structures.

Watterson [10] states that chlorpromazine produces depersonalization with visual hallucinations in 15% of the patients maintained on this drug. There is a frequency and intensity in dreaming, with visual imagery consisting chiefly of series of scenes from childhood and bizarre and startling apparitions.

In a description of visual toxicity of methanol, Potts [11] outlines the clinical aspects of experimental poisoning. Luvoni and Penzani [12] describe the toxic action of trichlorethylene on the eye producing peripheral constriction and optic atrophy. Janssen and Böke [13] describe increase in visual disturbance in tuberculous meningitis since the introduction of isoniazed-streptomycin treatment. Bruce [14] tells of permanent bilateral blindness following the use of hexamethonium chloride. Hogan, Thygeson, and Kimura [15] describe the use and abuse of adrenal steroids and corticotropin therapy. Oehninger, Rodriquez Barrios, and Gomez Haedo [16] describe optic neuritis caused by arsenicals resulting in cloudy vision and field constriction treated successfully with dimercaprol (BAL).

Nutritional amblyopia found in prisoners of war continues to be reported. King and Passmore [17] describe vitamin B deficiency in American prisoners of war in Korea. Fisher [18] tells of residual neuropathologic changes in Canadian prisoners of war in Japan.

Miranda [19] describes internal ophthalmoplegia from lead intoxication with encephalitis. Brecher, Hartman, and Leonard [20] discuss the effect of alcohol on binocular vision. With rising levels of alcohol esophoria or esotropia develops for distance and exophoria or exotropia for near. The position of rest is at about 60 cm. This study supports the hypothesis that separate convergence and divergence mechanisms exist to control binocular vergence, since the suppression of these functions by alcohol causes the eyes to assume an intermediate or neutral position.

Peripheral Visual Pathway

Pathologic changes in the optic system in disseminated sclerosis are described by Lehoczky.[21] Hayashi [22] found demyelinization in the optic nerve of rabbits by employing injection of autogenous brain emulsion from experimentally produced acute disseminated encephalitis. Markham and Otenasek [23] describe a case of neuromyelitis optica simulating spinal cord tumor. Steinmetz and Kearns [24] use Hardy-Rand-Ritter pseudoisochromatic plates as a diagnostic aid in determining the presence of retrobulbar neuritis of multiple sclerosis. They describe this as a refined visual acuity test more sensitive than black and white.

McPherson and Ryan [25] describe papilledema in relation to intracranial lesions and outline the differential diagnosis. Another similar article is by Rintelen,[26] who describes the anatomy and various affections of the optic nerve in connection with diseases of the central nervous system.

An article on the optic nerve sheath pathway and its role in the spread of foreign bodies and tumor cells from the cranial cavity to the orbit is presented by Levine and Bronstein.[27] The authors believe that continuous patent passages exist between the subdural and subarachnoid spaces of the brain and sheaths of the optic nerve. While this is true beyond dispute for the subarachnoid space, anatomists and clinicians both question the patency of the extension of the sub-

dural space in the orbit and believe that there is a close apposition of the two sheaths, the dura and the arachnoid. These membranes may be separated by hemorrhage or exudate, which may occur as an isolated phenomenon or in conjunction with but not extension from intracranial hemorrhage. Hedges and Walsh [28] cite a case of optic nerve sheath and subhyaloid hemorrhage following angiocardiography and state that this can occur as an isolated bleeding, in the absence of subarachnoid cerebral hemorrhage, from intracranial venostasis resulting in rapid increase of intracranial pressure. Manschot [29] writes of intraocular symptoms from subarachnoid hemorrhage which extends along the patent optic nerve sheath to cause pressure on retinal veins as they traverse the optic nerve.

Berg [30] describes gliomas of the optic nerve in neurofibromatosis, and Love, Dodge, and Bair [31] tell of the complete removal of gliomas affecting the nerve. Bregeat, Fischgold, and David [32] describe radiography of chiasmatic glioma. Levitt [33] reports a case of primary glioma of the optic chiasm.

Some instructive manifestations of chiasmal disease is the subject of a discussion by Wendland.[34] Ramamurthi [35] relates the causes of optic chiasmal arachnoiditis as trauma and infection, chiefly meningitis produced by pneumococcus, tubercle bacillus, and Treponema pallidum. The symptoms are progressive visual loss and optic atrophy. Chiasmal arachnoiditis is a localized basal meningitis designated by its location. The various causes of meningitis apply to chiasmatic arachnoiditis.

There are two current papers on the lateral geniculate body. Vastola [36] studied the electric potential responses of the lateral geniculate body in the cat to stimulation of the optic nerve. Vrabec [37] traced the anlage of the lateral geniculate body through ontogenesis in eight human foetuses.

Blood Supply and Vascular Affections

Böck and Schwarz-Karsten [38] report further on their investigation of origin of the ophthalmic artery. The authors state that the ophthalmic artery leaves the internal carotid from its frontal and medial aspect immediately after it has passed the cavernous sinus and perforated the dura mater. In my study the ophthalmic artery not infrequently was found to leave carotid extradurally and proceed to the optic foramen without passing through the dura or sending vessels through. It definitely, in these instances, does not supply the intracranial portion of the optic nerve. A discussion on the variability of the origin of the ophthalmic artery is given by Linc, L. Puzanová, and A. Puzanov,[39] who relate its functional significance. François and Neetens [40] continue their excellent exposition of the vascularization of the optic nerve with the study of the intraorbital and intracranial portions.

A number of articles on aneurysm have been published during the past year. Larmore [41] discusses aneurysm of the ophthalmic artery. Offret and Massin [42] describe the development of intracranial aneurysms and their relation to the visual apparatus. Aneurysms of the internal carotid and its branches is the subject of Goddé-Jolly's [43] presentation. Holmes [44] describes the ocular symptoms of intracranial aneurysms. Intracranial aneurysms should be suspected when there is sudden onset of cranial nerve palsies with severe pain. If the carotid cavernous sinus is involved, the first symptom is usually synchronous pulsation of head and heart and unilateral exophthalmos. Clinical localization of intracranial aneurysms and vascular anomalies is described by Walker,[45] who studied 285

cases and classified the symptoms according to the site of lesion. Dany and Lobstein [46] report a case with bilateral iridoplegia and other symptoms with low retinal arterial pressure produced by aneurysm of the internal carotid artery. White and Adams [47] discuss combined supraclinoid and infraclinoid aneurysms of the internal carotid artery which involve the third, fourth, fifth, and sixth cranial nerves, with external and internal ophthalmoplegia, pain, and hyperesthesia of the face. The visual system may be implicated by extension, to produce monocular blindness. Caroticocavernous fistula without pulsating exophthalmos was the subject for discussion by Clarke, Beaconsfield, and Gordon.[48] They state that it occurs in 10% to 15% of the cases owing to reduction of return of blood on the involved side. Erdbrink [49] speaks of subclinoid or intracavernous aneurysm involving the nerves to the ocular muscles and sensory nerves to the face, eye, and orbit. He makes a plea for the use of angiography for diagnosis and localization.

A monograph has been recently published by Bonnet [50] on arterial intracranial aneurysms. The study is complete, and the book is well recommended. He also has an excellent article on the cavernous space and its syndromes.[51]

In a paper entitled "The Circle of Willis" Symonds [52] describes the ocular symptoms of occlusion of the internal carotid artery, with transient blindness due to retinal ischemia as the most prominent symptom. Frera and Papo [53] discuss the variations of the retinal arterial pressure in thrombosis of the internal carotid artery, citing 22 cases. There was considerable increase in pressure in the retinal artery in the eye on the side opposite to that with the sensory and motor disturbances, which showed a tendency to normalize with improvement of the neurologic disturbance.

Knudsen [54] tells of thrombosis of the internal carotid artery with collateral circulation through the ophthalmic artery. Christophe and Thiry [55] present a similar paper. Nielsen [56] writes of thrombosis of the internal carotid artery, describing ocular symptoms. Kríz [57] emphasizes the importance of electroretinographic examination in thrombosis of the internal carotid artery. Attempts to determine the collateral circulation by way of the ophthalmic artery with both eyes at rest and with compression of both common carotid arteries was the procedure in this examination. The ERG revealed a better blood supply on the right side. Taveras, Mount, and Friedenberg [58] demonstrate by arteriographic studies the external-internal carotid artery anastomoses by way of the ophthalmic artery. Calamandrei [59] writes of ophthalmological findings in cerebral angiography and Sachs,[60] reporting two cases, presents arteriographic demonstrations of the collateral circulation through the ophthalmic artery in internal carotid artery thrombosis. Bonnet and Bret [61] describe tomography of the internal carotid artery.

A case of persistent carotid-basilar anastomosis associated with aneurysm of the homolateral middle cerebral artery with oculomotor paralysis was presented by Murtagh, Stauffer, and Harley.[62]

A case of ocular manifestations in a patient with hemorrhage into the fourth ventricle was presented by Sengupta.[63]

Cerebral Visual Areas

There has been a number of publications regarding the cerebral visual areas and their functions—reception, interpretation, and disposition of visual stimuli. Christensen,[64] in his thoughts and remarks on vascular stereoscopic vision, believes the optic pathways do not join before reaching the striate area of the

occipital lobe where they form the "cyclopic cerebral eye." Dieterle and Babel [65] discuss the diagnostic importance of simultaneous registration of the electroretinogram and of the EEG (determination of the retinocortical time) in affections of the optic pathways. Rønne [66] states that normal binocular vision (fusion and stereopsis) arises from integration of retinal stimuli taking place in the occipital center. The observation of simultaneous cessation of retinal rivalry and disappearance of sensory fusion and stereopsis during intoxication supports the view that integration and suppression are virtually complimentary expressions of one and the same basic process. The inhibitory activity, as abnormally demonstrated in retinal rivalry, must be looked upon as a prerequisite for the binocular integration of disparate stimuli.

The eye centering system is discussed by Bender.[67] He states that the straight-ahead stare is found in epilepsy (grand and petit mal), diseases of the basal ganglia, and post encephalitis conditions. These conditions damage the ocular centering areas and abolish the quick phase of induced or spontaneous nystagmus but do not affect, as a rule, conjugate deviation.

Impaired scotopic vision was found in adiposogenital dystrophy and is reported by Landau and Bromberg,[68] who suggest that the mechanism of scotopic vision may be related to the function of the hypothalamus.

Granit [69] has recently published a book on receptors and sensory perception. It should be well received and read with interest.

In considering the aphasias of visual implication, a good introduction can be had by reading an excellent article by Riese [70] on Hughlings Jackson's doctrine of aphasia and its significance today. Schuell [71] has an article on diagnosis and prognosis of aphasia in which he discusses involvement of audition, vision, and the sensory motor systems in the language process in reference to reading, speaking, writing, and understanding. When there is specific visual involvement, recovery of speech is good but recovery of reading and writing is slower.

Pallis [72] describes a patient with an embolus in the right posterior cerebral artery found at angiography. The patient had bilateral superior homonymous quadrantanopsia, color blindness, inability to recognize faces, and disruption of spatial thought. He did not recognize his wife and doctor but could recognize animals. Duensing [73] writes of optic spatial agnosia resulting from occipital lobe trauma, reporting two cases. De Busscher [74] relates symptoms of visual agnosia with regard to moving and immobile objects and incomplete achromatognosia after two vascular lesions in a hypertensive patient. Left homonymous hemianopia and right upper quadrantanopia were present.

Berlin [75] cites a patient who was unable to close his eyes when awake although they closed in sleep. There was a right cerebral lesion and left hemiplegia.

Nielsen [76] discusses dreams and psychosis in occipital lobe affections. He states that, since the occipital lobe is essential to visual recognition and revisualization, the decortication of the convex cortex of one occipital lobe to remove the revisualization area (of dreams and old memories), which is the trigger center for psychogenic processes, might be a sastisfactory treatment for schizophrenia.

Strazzi and Gaist,[77] in an earlier report, tell of the neurovisual consequences of occipital lobectomies with disturbance of receptive and psychic visual function.

Dream recall and eye movements during sleep are discussed by Dement,[78] who studied the condition in schizophrenia and normals. Bursts of motility,

probably representing single dream episodes, may be more pronounced in schizophrenia.

Dewhurst and Pearson [79] tell of visual hallucinations of the self (autoscopic) in organic disease, stating that the precipitatory factor occurs only among those with highly developed visual memory sense of their corporal being. The lesions were produced chiefly from tumors, injuries, and infections found in the temporal, parietal, and occipital lobes. Lilliputian hallucinations, writes Goldin,[80] can be caused by a variety of affections and can only be precipitated by a person with a paranoid personality trait plus an unresolved unconscious conflict.

Glezerov [81] tells of the peculiarities of the functional changes in lesions of the visual cortex. Schlaegel and Quilala [82] describe hysterical amblyopia. They found tubular fields in both functional and organic conditions. Tubular fields of hysteria are circular with sharp borders and remain the same size, independent of distance.

Visual imagery and electroencephalographic changes are described by Walter and Yeager,[83] who noted affections of visual imagery and recall. Visuomotor performance was studied in 180 psychiatric patients and 15 blind adolescents.

Visual Fields

A number of authors discuss field studies with flicker stimuli. Collins-Garston [84] describes the influence of characteristics of a fluctuating visual stimulus in flicker sensation. Kleberger [85] believes that flicker is more sensitive than ordinary targets in perimetry and discusses his findings in normal and abnormal vision. Mahneke [86] describes the flicker-fushion threshold. Watanabe [87] tells of encephalographic studies induced by flicker illumination. A review on optic and visual physiology, including the subject of perimetry, is given by Miles.[88]

François and Verriest [89] describe perimetry of the dark-adapted eye. Harrington and Hoyt [90] discuss ultraviolet radiation perimetry with monochromatic blue stimuli, which detects early defects in conduction fibers of the retina and optic nerve. Berk [91] presents a critical evaluation of color perimetry. He demonstrates the decrease of visual field when induced by color targets under standard testing procedure, which he states is the result of the decrease in light intensity. This supports the contention that the size of the visual field is subject to light intensiy and not color. Many neurologists and ophthalmologists still retain the preconceived idea that color fields are of diagnostic and localizing value. This remains a controversial subject, with an inclination toward the belief that size and illumination, rather than color, are the factors which determine the extent of the visual field.

Dubois-Poulsen and Magis [92] cite the case in which scotomas are localized in the vertical dividing line of the visual field as a result of interhemispheric occipital lesions, with report of two cases. The symptoms produced by the occipital lobe lesion are agnosia for colors, defects in stereoscopic vision, quickening of eye movements, slow recognition of objects in one-half of the field, and difficulty in avoiding objects.

Gunkel and Ryan [93] present a self-recording remote-control tangent screen, and Hagedoorn and van den Bosch [94] present a double projection campimeter.

A permanent homonymous migraine scotoma was found in a patient by Robinson.[95] Scintillating scotoma appeared, followed, after one attack, by homonymous paracentral scotoma and, finally, by complete homonymous hemianopsia which cleared to a homonymous right superior quadrantanopsia.

An exceptionally good book on visual fields has been written by Hughes,[96] who very successfully integrates the subject for the benefit of the ophthalmologist and neurologic specialists.

The Oculogyric System

Hedges and Adler [97] describe the oculomotor manifestations of lesions in the brain stem in three cases; one of unilateral internuclear ophthalmoplegia, the second of bilateral internuclear paralysis, and the third of paralysis of the vertical movements. Ethelberg [98] discusses vestibulo-ocular reflex disorders in a case of supratentorial metastatic tumor which produced transtentorial herniation and foraminal impaction of the brain stem. He believes that the abnormal caloric manifestations are the result of reticular rather than posterior longitudinal bundle damage. Cooper, Daniel, and Whitteridge [99] describe muscle spindles in the human extraocular muscles which are termed proprioceptor receivers and which are also projectors of reflex activity in association with the brain stem and cerebellum.

Holmes [100] describes hereditary congenital ophthalmoplegias and suggests (1) developmental causes due to aplasia or displasia of the nuclei, the muscles, or higher cerebral centers or (2) pathologic involvement with degeneration. He further commends consideration of heredity, with abiotrophic or dystrophic changes as causative factors.

Murray [101] describes in 122 patients under 16 years of age symptoms of restricted ocular motility from acquired disturbances. The conditions excluded from this subject were congenital or developmental affections, local involvement of nerve or muscle, and poliomyelitis. The studies were made of third and sixth nerve paralysis, supranuclear palsies, seventh nerve paralysis, and myasthenia gravis. He concluded that the sixth nerve paralysis might be of localizing value, not necessarily the result of increased intracranial pressure. He found that intracranial tumors accounted for about 70% of eye muscle involvement in children, a much greater percentage than in adults, where multiple sclerosis or vascular lesions predominate.

Paralysis of lateral conjugate eye movements may be the only focal sign of bulbar poliomyelitis. This condition is discussed by Adler, Landau, and Robinowitz.[102] They place the possible site of the lesion in the pons, with involvement of the vestibular and abducens nuclei, in addition to implication of the mechanism for control of lateral gaze.

Piper [103] tells of congenital gaze paralysis as a fixation of primary function. He believes that this inability to fix for distance is probably due to arrested development. Three cases are described. Significance of congenital cyclovertical motor defect is described by Urrets-Zavalía,[104] who states that variations exhibited by horizontal deviation in pure elevation and depression, as well as the vertical imbalances, are thought to be of developmental origin. A description of the anatomical structures of the oculogyric system is given by Solbach and Schmitz,[105] who apply this knowledge to clinical findings and postmortem examination of 22 patients.

Fuldner,[106] in an article "Cerebral Palsy: Where Next?" writes of the concurrence of paraplegia and retrolental fibroplasia which appear attributable to a common basis in prematurity. He cites five cases with birth weight of from 1.12 to 3.00 pounds.

In a series of 100 cases of cerebral palsy Breakey [107] found 56 showing ocular symptoms, among which were 40 with esotropia.

Electro-oculographic studies were made of eight patients with ocular palsies by Francois and De Rouck.[108] Characteristic tracings were found for various types and stages of involvement.

Vascular phenomena involving brain stem structures are discussed by Fang and Palmer,[109] who emphasize, in addition to hemiparesis, conjugate gaze palsies and visual impairment, which occur more frequently than is generally recognized. A syndrome of intermittent insufficiency of the basilar arterial system with periodic transient episodes of dysfunction is presented by Siekert and Millikan.[110] The symptoms resulting from ischemia are dimness of vision, diplopia, vertigo, confusion, etc. Kearns, Wagener, and Millikan [111] present a patient with homonymous hemianopsia, nystagmus, and internuclear ophthalmoplegia with unawareness of blindness. This last symptom when combined with bilateral hemianopsia, mental deterioration, and amnesic aphasia is called Anton's syndrome.

Guibor [112] discusses cerebral palsy, suggesting a practical routine for discerning oculomotor defects in cerebral palsied children. He finds that more than 50% have ocular defects. Tests are suggested for determining palsies in early childhood.

Ophthalmoplegic migraine is classified by Remky [113] into (1) simple angiotonic or angiospastic; (2) migraine plus ophthalmoplegia: (*a*) spastic circulatory with miosis, scotoma fugax with good eye movement, and (*b*) hypotonic circulatory disorder with mydriasis and external ophthalmoplegia, and (3) cerebral symptoms of muscle paralysis from increased pressure.

In an article by Bonnet [114] on paralysis of the abducens nerve the intracranial and intraorbital affections were discussed and grouped according to location and syndromes in a very comprehensive study. Bedrossian [115] presents the case of a diabetic with abducens paralysis who past pointed when the affected eye was covered. The reason for this phenomenon was discussed. A case was reported by Love and Hollenhorst [116] of bilateral abducens paralysis with intense headaches produced by a cyst in the septum pellucidum (fifth ventricle) cured by pneumoencephalography.

There are several reports on myasthenia gravis. Ferguson, Hutchinson, and Liversedge [117] in a survey of 85 cases conclude that thymectomy is not necessarily a consideration. If the condition is initially confined to the ocular muscles and remains localized for two or three years, they conclude that there is reasonable chance that the affection will not spread and will produce very little serious difficulty. The ocular symptoms of myasthesia gravis are also discussed by Francois, Begaux, Decock, Stefens, and De Rouck.[118] Ocular symptoms are the first signs in more than half of the cases. Ocular involvement occurs in most of the cases of long standing, marked by exacerbations and recessions aggravated by fatigue. The duration is from death within several years, in acute forms, to chronicity of many years. Ptosis, usually bilateral, is the commonest symptom. Intrinsic muscles usually are not affected. Vergence may be weakened; version and duction may be impaired. A case of myasthenia gravis with retraction of the upper right lid and ptosis of the left is presented by Galvez.[119] Edrophonium (Tensilon) is recommended by Boruchoff and Goldberg [120] as an aid to diagnosis of ocular myasthenia gravis. It is safe and rapid-acting as a direct stimulant to the myoneural junction.

Vergence

Breinin [121] reveals the nature of vergence by electromyographic studies. He concludes that divergence impulses pass to the two lateral recti muscles equally

but are neutralized in the fixating eye by an opposing version in the maintenance of fixation. The deviating eye is stimulated by both divergence and version.

Spasm of the near reflex is the term applied by Cogan and Freese [122] to the intermittent, usually painful, excessive action of convergence and accommodation with miosis. Sixteen cases were studied in detail. Functional disturbances are the rule. The occurrence is most frequently in adolescent girls.

Spasm of fixation resulting from birth injury is described by Alfano,[123] who believes that the cause is the result of damage to the frontal oculogyric centers by hemorrhage from the superior longitudinal sinus from birth injury. The effect of version and vergence movements on ocular torsion is described by Pascal.[124] He states that torsion takes place on oblique version and in convergence, but in opposite directions. The action on the vergence mechanism under the influence of alcohol is reviewed under Toxic Affections (see page 769 and Reference 20).

The Autonomic Nervous System—Intraocular Muscles

In a book, "The Eye and Midbrain," Thiel [125] describes the association of various reflexes, particularly those of the autonomic nervous system, and their effect upon the intraocular pressure in the production and control of glaucoma. This subject, in connection with the thalamus, has been presented from time to time. In the long search for the cause of so-called primary glaucoma the diencephalon is again being studied further.

In an article on brightness stimuli and the diencephalon Schmerl [126] states that the stimuli of light and smell reach the hypothalamic vasomotor centers, which release vasoconstrictor and vasodilator activities influencing intraocular pressure.

Lowenstein [127] discusses benign postinfectious disorders of the anterior midbrain in the production of alternating contraction anisocoria combined with general fatigue and peripheral neuritis. This anterior midbrain symptom was the only sign of encephalitis in the study of 22 patients.

Using the infrared technique which he developed, Lowenstein [128] has established syndromes produced by lesions of the peripheral and central nervous systems in which 18 topical locations were typed. Lowenstein [129] presented a pupillographic instrument which he developed to record and analyze pupillary movements and reflexes.

The pathway for darkness and reflex pupillary dilatation is the subject of Arieff,[130] who examined 19 patients having complete cervical cord lesions. Stimulation above the lesion with a painful faradic current failed to produce pupil dilatation, whereas stimulation below the lesion produced dilatation. This tends to prove that, in man, dilatation due to pain is sympathetic in origin. In the same patients dilatation to darkness was found, proving that the undisturbed parasympathetic reflex was the producing mechanism. Deductions from this discussion were that the only reflex transmitted by the sympathetic fibers in man is the ciliospinal reflex. All other pupil dilatations are produced by parasympathetic activity.

In a report of 14 cases Casanovas [131] describes Adie's syndrome and reviews the literature.

The course of the fibers of intrinsic motility, the pupillomotor fibers in the third nerve, with anatomic and histologic study and pathologic description is presented by Lazorthes, Pigasson, and Gaubert.[132] The oculomotor nerve conveys fibers (constrictoparasympathetic) to the intrinsic eye muscles, which, because of their

surface location and vulnerability, are liable to pressure from the clinoid process and posterior cerebral and posterior communicating arteries. These points of contact and, in addition, the free rim of the cerebellar tentorium are the locations where the oculomotor nerve is compressed by increased intracranial pressure from above or from below (see section on trauma).

Mancall [133] reports a case of opticociliary neuritis, a combination of optic neuritis and internal ophthalmoplegia. The question as to the location of the lesion, or possibly two lesions, is discussed. The effect of retrobulbar injection of procaine on the optic nerve is described by Carroll and de Roetth.[134] There is reduction of vision within a few minutes after injection. No harmful effects are noted. Hilding [135] reports reduced intraocular tension after retrobulbar injection. He also found reduction of vision and visual fields. In a discussion of the pharmacodynamics of the ciliary ganglion Weinstein [136] states that pupillomotor and vasomotor fibers have synapses in the ciliary ganglion. Inhibition of the ganglion function produces dilated pupil, paralyzed accommodation, and decreased intraocular pressure.

In a series of experiments on the eyes of cats, Melton, Purnell, and Brecher [137] found that the radial ciliary muscles responded to parasympathetic and sympathetic stimulation in opposite directions; so the action of accommodation can be explained, at least in part, by the direct action of these autonomic nerves on the radial muscle fibers of the ciliary body.

Nystagmus

Piesco [138] discusses the clinical significance of nystagmus. He states that if it is spontaneous in only one direction or is due to vestibular hyperexcitability it is of no diagnostic value. It is strongly suggestive of a midline lesion in the posterior fossa (*a*) if the nystagmus is spontaneous in several directions, (*b*) if there is also conjugate deviation of the eyes, (*c*) if there is positional or perverted nystagmus, and (*d*) if the rapid component is absent in induced nystagmus.

Disturbances of caloric and optokinetic nystagmus associated with localized lesions in the cerebral hemispheres are discussed by Carmichael, Dix, and Hallpike.[139] Neurogenic nystagmus is described in a monograph by Ohm,[140] who discusses types of vestibular, ocular, and optokinetic nystagmus, congenital and acquired. There is an excellent description of the anatomy and function of the brain stem.

Forsythe [141] presents five patients with congenital hereditary vertical nystagmus, a condition which is very rare. The actual type and site of the lesion producing the condition is not known. Westheimer [142] presented a case of voluntary nystagmus, which was produced only with marked convergence. One can recall that retraction nystagmus is also produced with marked effort of convergence, and so the lesion producing this symptom may lie in the hypothalamus or upper midbrain. Nathanson, Bergman, and Bender [143] describe monocular nystagmus and suggest the anatomical site for a lesion producing these conditions. Three cases are presented and discussed in detail. The nystagmus was stopped by barbiturates and closing the eyes. It was not affected by darkness. Induced vestibular and ocular nystagmus gave no constant findings.

The physiology of optokinetic nystagmus is discussed by Mackensen.[144] He states that the amplitude and frequency estimations are only of value in the median range of oscillation. With nystagmographic studies, Åschan and Bergstedt [145]

describe nonvestibular nystagmus. They describe ocular movements produced by the eye, optic nerve, and muscles and by central nervous connections. The nystagmus is divided into fixation and gaze types. Fixation nystagmus disappears in the absence of fixation, whereas vestibular nystagmus becomes more pronounced. Induced vestibular nystagmus with fixation nystagmus has two patterns; induced vestibular nystagmus with spontaneous vestibular nystagmus has but one. Spontaneous vestibular nystagmus can be revealed by terminating fixation, thus abolishing fixation nystagmus. Björk [146] describes the pattern of electromyographic studies of the extraocular muscles in optokinetic nystagmus and in reading. He states that an increase of activity in the agonist and a concomitant inhibition of activity in its antagonist are the usual findings. Electromyographic studies consistently demonstrated this in reading, movement of gaze, and nystagmus.

Under the section on trauma see a discussion of optokinetic nystagmus in patients with cranial trauma.

Kleiner and Roelofs [147] have written an interesting book on optomotor reflexes and nystagmus, in which they present new concepts. Some of the studies are based, in part, on 55 cases with various forms of nystagmus.

Intracranial Tumors

An important review by O'Rourke and Schlezinger [148] of a series of patients with a variety of brain tumors gives percentages of occurrences compared with those of Cushing. The discrepancy is obviously due to the fact that patients with predominantly eye symptoms are usually first seen by an ophthalmologist and those with other neurologic symptoms foremost are seen by the neurologist or neurosurgeon. There is an excellent description of clinical symptoms produced by the various tumors.

In a study of ocular manifestation of lethal midline granuloma, Cutler [149] described two cases. Birge [150] discusses meningiomas as an ophthalmologic problem. He states that frequently the earliest symptoms are field changes, usually homonymous hemianopsia and unilateral optic atrophy.

In a review of 156 cases, Chamlin, Davidoff, and Feiring [151] discuss changes produced by pituitary adenomas, eosinophilic and basophilic, and craniopharyngiomas. The authors list and describe ophthalmologic symptoms, the most frequent being visual field defects and optic atrophy with loss of central visual acuity. Del Castillo [152] also describes ocular symptoms of hypophyseal affections.

False localizing signs of intracranial tumors are discussed by Dodge, Clark, Wagener, and Hustead.[153] If symptoms appear before increased intracranial pressure develops they are usually of localizing value. If they are found after increased pressure, further study is necessary and the symptoms or signs may be of no localizing or diagnostic value; in fact, they may be of false localizing value. Examples are abducens involvement from displacement of the brain stem and oculomotor paralysis from displacement of the uncus of the temporal lobe.

A syndrome of increased intracranial pressure without localizing signs is described by Berg, Rosomoff, Aronson, Siebermann, and Pool,[154] in which the only symptoms are headache and papilledema. False signs as the results of increased pressure may lead to confusion. In this series lateralizing tumors predominate, although midline obstructive lesions and serous meningitis are usually reported as the cause of this syndrome. Ventriculography and arteriography and

other aids may establish the proper diagnosis. Once again, the plea is for early consultation, which may reveal symptoms leading to proper diagnosis.

Syndromes

Syndrome articles are collected under this heading, although they might very well be separated and assigned to the section or structure predominately affected. A few are so included. However, it is thought best, as they combine a number of symptoms, frequently of diverse nature and involving separated structures, to group them here.

The Foster-Kennedy syndrome and its etiology are well described by François and Neetens,[155] and its incidence is discussed by Diez.[156] Albert and Aznorez [157] present a patient with edematous intracanalicular optic neuritis and state that the Foster-Kennedy syndrome should not be considered pathognomonic of intracranial lesions. Frezzotti,[158] in his discussion of the localizing value of the Foster-Kennedy syndrome, emphasizes the point that the lesion is not always on the side of the greatest optic atrophy.

Feldman, Landau, and Halpern [159] describe a case with papilledema, a symptom of rare occurrence, which continued for 18 months in a patient with Guillain-Barré syndrome. The authors believe that this is probably due to increased protein content of cerebral spinal fluid with defective absorption.

Syndromes of the cavernous area are described by Bonnet,[160] with involvement of the internal carotid artery, venous plexus, Gasserian ganglion and its branches, and nerves to the ocular muscles. Abrahamson and Bell [161] describe the carotid cavernous fistula syndrome.

Raeder's paratrigeminal syndrome is described by Cristini.[162] The lesion is located in the midcranial fossa, involving the sympathetic fibers in the carotid-Gasserian tract, and is characterized by anesthetic neuralgia of the ophthalmic division and a spurious Claude Bernard-Horner syndrome. The lesion may extend to involve other cranial nerves and may produce a pure Claude Bernard-Horner syndrome.

Nonnenmacher [163] describes the syndromes of Sturge-Weber, Klippel-Trenaunay, and Parks-Weber, all of which are related, showing hereditary abnormalities of the vascular system in organs of ectodermal origin. Cogan and Adams [164] describe Balint's syndrome with ocular motor apraxia, collecting a series of 14 reported cases. Lebensohn [165] describes a case of Parinaud's syndrome. The paralysis of vertical gaze was produced by obstetrical trauma. Recovery occurred.

Haynes [166] made a quantitative investigation of the Marcus-Gunn phenomenon and suggests a possible cause, which he believes may be aberrant association of the trigeminal and oculomotor nerves or a lesion in the fibers in the brain stem innervation of the motor nuclei controlling vertical gaze.

Möbius snydrome, congenital oculofacial paralysis or facial diplegia, is discussed by Sprofkin and Hillman,[167] by Bedrossian and Lachman,[168] and by Evans.[169] The etiology is considered—whether it be nuclear aplasia or hypoplasia, nuclear degeneration, or muscular aplasia. Nisenson, Isaacson, and Grant [170] report three cases with bilateral abductor and facial paralysis.

Gougnard-Rion and Paris [171] present a case of heterochromia with Claude Bernard-Horner syndrome. Heterochromia appears to be more frequent in congenital lesions. The significance of temporary and alternating ptosis, miosis, and

anhidrosis is related by Freeman and Russell,[172] who describe a patient with cystic cavitation in the cervical cord resulting from trauma. When the cavity is filled, Horner's snydrome is produced; when it is emptied by drainage or change of position, the syndrome disappears.

Pallis and Fudge [173] describe the neurological complications of Behcet's syndrome with ulcerative mouth and genital lesions. The eye symptoms are iritis and uveitis with intraocular hemorrhage and, less frequently, optic neuritis. Brain stem symptoms are present, with paralysis of ocular muscles for both version and duction. Meningeal or encephalitis symptoms may occur with confusion.

Adie's syndrome is discussed under Pupil.

Trauma

Trauma plays a considerable role in neuro-ophthalmology. Head injuries are seldom without damage to the ophthalmologic structures. Even remote body injuries, through various causes, produce serious visual disturbances. Neck or cervical injuries (whiplash) are on the increase. For these reasons I believe that trauma warrants a section of its own.

There are several reports on optic nerve lesions in head injuries. Landolt,[174] in a report of 19 cases of fracture of the lesser wing of the sphenoid, states that the wall of the optic foramen is involved in 75% of the cases, producing direct trauma and/or edema and hemorrhage in the optic nerve or hemorrhage in the nerve sheath. Brihaye [175] writes of lesions of the optic nerve in closed trauma to the skull, giving a review of the anatomy and various types of trauma, mechanical and vascular, with suggestions as to treatment.

Traumatizing damage to the chiasm, reported by Zintz,[176] results in sagittal tears and not injury by bone spicules. Field defects show bitemporal loss as the rule, although binasal loss may occur if the vessels situated lateral to the chiasm are involved. This report recalls the study of Evans and Browder [177] in 1944, who described the problem of split macula.

A case of post-traumatic cortical blindness is presented by Rosenberg.[178] In this patient the pupils reacted normally; the fundi were normal. The symptoms were anosognosia with confabulation, poor appreciation of objects in space, poor recollection of color, and incomplete right hemianopsia.

In an article on ocular palsies and automobile accidents Hambresin [179] states that the third nerve is most frequently affected, being damaged at the petrosphenoidal ligament (Grubers' ligament) or at the posterior clinoid process. In a series of cases he found Horner's syndrome was produced in 14.8%. Visual disturbances were rare. Lazorthes [180] discusses total paralysis of the third nerve with unilateral mydriasis in cranial trauma with temporal involvement. He states that the usual cause is pressure of the nerve against the posterior clinoid. In my studies [181] it was found that most frequently the oculomotor nerve would be compressed against the edge of the rigid shelf of the cerebellar tentorium by the uncus of the temporal lobe in transtentorial herniation following injury which had produced edema and hemorrhage in the temporal lobe. Occasionally the brain stem would be pressed upward against the tentorial rim by a space-consuming lesion below to produce oculomotor damage.

Anderson [182] discusses optokinetic nystagmus in patients with cranial trauma, stating that a unilateral absence of optokinetic nystagmus is a valuable finding,

as it renders certain diagnosis of a lesion in one cerebral hemisphere if hemianopsia or other clinical symptoms are present.

Injuries of the trigeminal nerve, its ganglion, and its divisions are discussed by Jefferson and Schorstein,[183] who reported a study of 66 cases. Neuroparalytic keratitis was recorded in only a small proportion.

So-called whiplash injuries, produced by a jerking of the head backward from a sudden bump from behind, are becoming more prevalent with the increase of automobile accidents. The ophthalmologic symptoms are discussed by Middleton.[184] Damage to the cervical sympathetics produces Horner's syndrome or sympathetic ophthalmoplegia. Occasionally trauma to the brain stem or cervical cord may involve the sympathetic fibers along with other cranial nerves and motor sensory tracts. Visual complaints and considerable mental disturbance are often present, with stiff neck muscles, occipital pain, and tenderness.

Miscellaneous

Herpes zoster ophthalmicus occurs rarely during early childhood. Poulsen[185] found only 18 reported cases of patients under 12 years of age. The condition usually runs a benign course in children. Albert and Aznarez[186] tell of neuroparalytic keratitis following operation for trigeminal neuralgia. The authors believe, and I concur in their assumption, that the condition is a manifestation of atrophic disturbance in the sympathetic innervation of the cornea. They advise systemic vitamin therapy and local protective medication. In my experience, we thought it best to use artificial tears of some sort if the Schirmer test indicated reduced lacrimation, as it often did. We thought amino acid ointment, containing nutrient chemicals, might be of some benefit for local use. Why some eyes went on to total destruction and others suffered slight annoyance for a week or two, from the same operation, we were unable to determine. Cortisone is recommended in the treatment of herpes zoster ophthalmicus by Scheie and Alper,[187] who have witnessed rapid improvement with suppression of inflammation. However, this treatment is not curative.

One hundred cases of Bell's palsy are reported by Taverner,[188] who finds that the prognosis can be determined by electromyographic study. Failures show fibrillation on the electromyogram and display erroneous associated movements, contraction of the face, crocodile tears, and bursts of blinking. The etiology remains obscure. The cause, according to Taverner, may be a severe widespread parenchymatous neuritis. Unger[189] stresses the importance of recognizing the fact that Bell's palsy, and affection of other cranial nerves, may be symptoms of poliomyelitis.

In a discussion of physiological abnormalities in agenesis of the corpus callosum, Russell and Reitan[190] list impaired visuomotor coordination with impaired intelligence and emotional instability.

The condition of porencephaly is reviewed and discussed by Alper and Dessoff,[191] who present one case. They state that the condition may be differentiated and diagnosed by pneumoencephalography or ventriculography.

Laitinen, Miettinen, and Sulamaa[192] write of ophthalmological observation in craniosynostosis, in which exophthalmos and strabismus due to deformities and papilledema, caused usually by increased intracranial pressure, are frequent findings. Optic atrophy and blindness usually results if there is not early surgical intervention.

Yourish, Wollin, and Nathaniel [193] note increasing reports of vascular neoplasms as causative factors in syringomyelia. Dilated and tortuous conjunctival and retinal veins were noted in the case they presented with a saccular aneurysm in the fundus of the right eye. Horner's syndrome and rotatory nystagmus were also present.

Tuberous sclerosis is discussed by Pagenstecher,[194] who gives a historic review and presents two cases of this congenital syndrome, which includes affections of the skin, nervous system, and eyes predominately, with less frequently involvement of the internal organs of the body.

The ocular sequelae resulting from tuberculous meningitis pose new problems, according to Mooney.[195] This is due to the remarkable results in the treatment of this dreaded disease. The patient, who now survives, may be left with tuberculous arachnoiditis, which requires treatment if vision is to be saved.

Jefferson [196] discusses the clinical correlation between encephalopathy and papilledema in Addison's disease. He states that suprarenal failure is causally related to edema of the brain and papilledema.

There are a number of articles on exophthalmos. Smelser and Ozanics [197] discuss the nature of the exophthalmos-producing principles in pituitary extracts and the possibility of other factors as causative agents. Hedges and Scheie [198] tell of visual field defects in exophthalmos associated with thyroid disease. Reporting six cases, they believe that the field loss is primarily due to optic nerve involvement in the orbit as the result of pressure. Oculomotor disturbance, particularly paralysis of one or both superior recti muscles, is related by Börner.[199] Visual changes in progressive exophthalmos are described by Igersheimer,[200] who believes that direct pressure on the optic nerve or to its nutrient vessels accounts for the field defect and visual loss. Hypophysectomy for malignant edematous exophthalmos is discussed by Albeaux-Fernet, Guiot, Braun, Cauvin, and Romani.[201]

The ocular significance of intracranial calcium deposits is presented by Alfano and White,[202] who describe the various normal and abnormal conditions in which these deposits occur, with description of the disease and location.

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Correspondence

AQUEOUS HUMOR OUTFLOW: AN EXPERIMENTAL STUDY USING RADIOPAQUE MATERIALS

To the Editor.—In the June, 1956, issue of the ARCHIVES Mr. Bruce Cohan published a paper on his experiments using radiopaque materials to follow the outflow of aqueous from the anterior chamber of rabbits.

Mr. Cohan is a very bright young man and his advisors at the University of Michigan are most able. These sort of experiments are certainly needed. The trouble in this case is that he set out to prove a theory that may or may not be true. He wanted to show that the aqueous is eliminated through the "aqueous veins" and therefore his interpretation of the obtained images is biased. To interpret this sort of indefinite image is very difficult anyway and imagination plays an unduly great role. It may be made from entirely different points of view and so lead to entirely different results.

I happened to be present at the Toronto meeting where he projected these photographs on the screen, making them better visible than the published reproductions in the ARCHIVES. There I pointed out that on Mr. Cohan's eight-minute film the opaque material flows into the ciliosclera1 sinus at several places, in far wider patches than 10 "aqueous veins" put together. On his 30-minute film a clear band was seen between the opaque material in chamber and a similar opaque band resembling the position and width of the ciliary body. This can be interpreted as proof that the opaque material is taken up by the vascular bed of the ciliary body, and not by the "aqueous veins." That some of this material found its way into the "aqueous veins" is possible. But that the main outflow is not through these channels is very probable.

If we shall set out to prove or disprove certain theories we shall be misled by our ardent desire to do so and will suggest ourselves the wrong interpretation of our results. We must fight off the human element of wishful thinking and try to find the truth which is evasive and mysterious.

FRANK A. VESEY, M.D.
Toledo 10, Ohio

Obituaries

DR. HENRY COOPER HADEN

1873-1956

Henry Cooper Haden was born in Galveston, Texas, Dec. 7, 1873, the son of Dr. John M. Haden and Sarah Brannum Haden. He died April 24, 1956, after a lingering illness.

Dr. Haden's father was a medical officer in the Confederate Army and for a while served as Surgeon-General. Dr. Haden took great pride in a framed testimonial to his father signed by hundreds of Galveston people in appreciation of his being able to keep yellow fever out of the city when it was in all the neighboring cities. Much of Henry's boyhood was spent in Tennessee, where he attended Sewanee Military Academy as a schoolmate of the late Dr. Edward C. Ellet.

HENRY COOPER HADEN, M.D.
1873-1956

Dr. Haden graduated in medicine at the University of Pennsylvania in 1895. There he came under the influence of Dr. George de Schweinitz and worked as his assistant several years. After a period of study in Vienna he returned to Galveston as Head of the Department of Ophthalmology and Otolaryngology at the University of Texas Medical School. In 1917 Dr. Haden entered the Army and was made Chief of the Division of Ophthalmology at Walter Reed Hospital. After the armistice he moved to Houston, where he practiced until his retirement. During these years of active practice Dr. Haden devoted all his spare time to research on embryology of the eye. He enriched the literature by many contributions on the development of the human eye and adnexa, among them the Sixth de Schweinitz Lecture and an address before the St. Louis Ophthalmic Society. His earlier writings concerned the early diagnosis of glaucoma, a subject in which

he was always vitally interested. Dr. Haden possessed one of the finest collections of slides of embryological specimens in the world. He left these to the Department of Ophthalmology of Baylor University College of Medicine, in which he had been greatly interested. Dr. Haden was a member of all his local and state societies as well as the American Academy of Ophthalmology and Otolaryngology and the American College of Surgeons. He was a member for many years of the American Ophthalmological Society and served as its president in 1947-1948.

Henry Haden, or "Harry," as his intimate friends knew him, insisted on the highest standard of ethics in medicine, and he made no compromises. Beneath a dignified and at times austere manner beat the kindest of hearts. One had to know this man well to appreciate the fineness of his character. It was my privilege to know him intimately and to call him friend. The thousands of patients who grieved over his retirement and death attest to the hold he had upon his people.

Dr. Haden married Blanche Randall in Trinity Church in Galveston Dec. 31, 1902, the church in which he was christened, confirmed, and from which he was buried. He is survived by Mrs. Haden, a daughter, Mrs. Albert Bel Fay, and three grandchildren.

EVERETT L. GOAR, M.D.
Houston, Texas

News and Comment

ANNOUNCEMENTS

Hemisphere Ophthalmologists to Hold Interim Congress in New York in April, 1957.—Plans are well under way for the Fourth Interim Congress of the Pan-American Association of Ophthalmology, which will be held in New York, April 7-10, 1957, with headquarters at the Hotel Statler.

Dr. Brittain F. Payne, New York, President of the Association, and Dr. Moacyr E. Alvaro, São Paulo, Brazil, Executive Director, have announced the appointment of the following local committees, with their chairmen: Program: Dr. John M. McLean, New York; Motion Pictures: Dr. Wendell L. Hughes, Hempstead, L. I.; Exhibits: Dr. Gerald E. Fonda, Short Hills, N. J.; Entertainment and Special Arrangements: Dr. Elizabeth Constantine, New York; Registration and Housing: Dr. Girolamo Bonaccolto, New York; Press and Public Relations: Dr. Frank Constantine, New York.

Acting in an advisory capacity to the planning committee are Drs. William L. Benedict, Rochester, Minn., Executive Secretary-Treasurer, American Academy of Ophthalmology and Otolaryngology; Daniel Snydacker, Chicago, former Acting Executive-Secretary for countries North of Panama; J. Wesley McKinney, Memphis, present Executive Secretary for North of Panama; Conrad Berens, New York, Past President; Algernon B. Reese, New York, Assistant Secretary-Treasurer, and Franklin M. Foote, Executive Director of the National Society for the Prevention of Blindness.

The Interim Congress will be a joint meeting with the National Society for the Prevention of Blindness. The eye specialists will hold sessions in the mornings, while the National Society will present its programs in the afternoon.

Hoppin Memorial Award.—An annual prize in commemoration of the late Judge William Warner Hoppin has been established by his family. The prize is to be awarded for the outstanding paper at the Residents Meeting, Section of Ophthalmology, New York Academy of Medicine. The advisory committee of the Section is to act as judge.

Judge Hoppin (1878-1948) was assistant United States Attorney General under Woodrow Wilson and was appointed Magistrate of the City of New York by Mayor LaGuardia.

As a member of the Board of Visitors of the Central Islip State Hospital and as secretary of the New York Association for the Blind (the Lighthouse), he was vitally interested in the field of ophthalmologic research and prevention of blindness. Ironically, he died in 1948 of cancer, as a result of metastasis of a malignant melanoma of the choroid.

The prize will consist of a scroll and cash award to be presented by Mrs. Hoppin at the fall meeting. The winning paper this year is "Carcinoma of the Meibomian Glands," by Bradley Straatsma, M.D., resident at the Institute of Ophthalmology, College of Physicians and Surgeons, New York.

Ophthalmology Course.—A basic course in ophthalmology will be made available to graduates of approved medical schools through University of California Extension on Wednesdays from 7:00 to 9:00 p.m. next Sept. 26 through May 29, 1957.

Sessions will be held in the Old Religious Conference Building, on the Los Angeles campus of the University.

The course has been planned to assist candidates in preparing for the American Board of Ophthalmology examinations and will offer a study of the basic subjects in ophthalmology as outlined in the syllabus prepared by the American Board of Ophthalmology, namely: Physiological Optics and Refraction, Embryol-

ogy, Histology, Anatomy, Chemistry, Physiology, Neurological Ophthalmology, Perimetry, and Pharmacology. This course is made possible through a grant from the Spratt Optical Company and the Superior Optical Company. Scholarships are available without charge to all qualified eye residents who wish to take the course.

Application forms for enrollment and detailed copies of class information are available on request to Medical Extension, University Extension, University of California, Los Angeles 24.

Course on Glaucoma.—A seminar on glaucoma with particular emphasis on gonioscopy and the study of the anterior angle will be given at the Brooklyn Eye and Ear Hospital on Nov. 12, 13, and 14, 1956. Ample opportunity for practical instruction in the use of the gonioprism will be given, and material from the glaucoma clinic will be utilized.

The course will be given by Dr. Daniel Kravitz, assisted by Dr. Mortimer A. Lasky, Dr. Arthur Shainhouse, Dr. A. Benedict Rizzuti, and Dr. Abner S. Rosenberg.

Registration is limited to six ophthalmologists only.

Application and the fee of $50.00 may be addressed to Dr. Daniel Kravitz, Brooklyn Eye and Ear Hospital, 29 Greene Ave., Brooklyn 38.

Postgraduate Series in Ophthalmology.—A series of teaching conferences planned especially for the ophthalmologist and conducted by the Section of Ophthalmology, Dr. Rocko M. Fasanella, Chairman, of the Yale University School of Medicine, will be held usually on alternate Fridays, 3:45-5:00 p.m., Nov. 9, 1956-March 29, 1957. The fee for the series is $15. Application for registration and fee should be sent to Dr. Arthur Ebbert Jr., Assistant Dean of Postgraduate Medical Education, Yale University School of Medicine, 333 Cedar St., New Haven 11, Conn.

The conferences are scheduled as follows:

Nov. 9—Psychological Considerations in Surgery. Irving Janis, Ph.D., Associate Professor of Psychology, Yale University. Comments by Theodore Lidz, M.D., Professor of Psychiatry, Yale University School of Medicine; Edith Jackson, M.D., Clinical Professor of Pediatrics and Psychiatry, Yale University School of Medicine.

Nov. 16—Reoperations and the Management of Complications in Glaucoma Surgery. Edmund B. Spaeth, M.D., Professor Emeritus, University of Pennsylvania Graduate School of Medicine.

Dec. 14—Lids and Facial Burns: Newer Concepts of Management. Donald P. Shedd, M.D., Assistant Professor of Surgery, Yale University School of Medicine.

Jan. 11—Surgery in Congenital Glaucoma. Harold G. Scheie, M.D., Professor of Ophthalmology, University of Pennsylvania School of Medicine.

Jan. 25—Keratoplasty: Reoperations and Management of Complications. R. Townley Paton, M.D., Clinical Professor of Ophthalmology, New York University College of Medicine.

Feb. 8—Eye Pathology—Some Unusual Cases. David Freeman, M.D., Assistant Clinical Professor of Ophthalmology, Yale University School of Medicine.

Feb. 22—Vitreous Transplants. Donald M. Shafer, M.D., Surgeon, Manhattan Eye, Ear and Throat Hospital.

March 8—Film: Embryologic Development of the Eye. Discussion by Leon S. Stone, Ph.D., Bronson Professor of Comparative Anatomy, Yale University School of Medicine.

March 29—Medical Management of Surgical Complications. Irving H. Leopold, M.D., Clinical Professor of Ophthalmology, University of Pennsylvania Graduate School of Medicine.

Course in Histopathology of the Eye.—An intensive course, making use of one of the world's largest eye collections, will be given Oct. 1-6, 1956, by Drs. Bernard A. Roberts and Lawrence Samuels, of the Department of Ophthalmic Pathology, New York Eye and Ear Infirmary, Brittain F. Payne, Director. Number of students will be limited. Write to Registrar, New York Eye and Ear Infirmary, 218 Second Ave., New York 3.

Call for Papers.—The 1957 meeting of the Section on Ophthalmology will be held in New York, June 3-7, 1957, simultaneously with that of the Association for Research in Ophthalmology.

Anyone wishing to present a paper before the Section is urged to communicate with Dr. Harold G. Scheie as soon as possible. A title and abstract of 50 to 150 words must be in his hands by Jan. 1, 1957. Anyone wishing to present a paper before the Association for Research should contact Dr. Lorand V. Johnson as soon as possible.

Lorand V. Johnson, Secretary, Association for Research in Ophthalmology, 10515 Carnegie Ave. Cleveland 6. Harold G. Scheie, Secretary, Section on Ophthalmology, 313 S. 17th St., Philadelphia 3.

New Eyes for the Needy.—New Eyes for the Needy, Inc., a nonprofit organization, staffed by volunteers, which is dedicated to improving the vision of needy people both here and abroad, will be represented for the second year at the Convention of the American Academy of Ophthalmology and Otolaryngology to be held at the Palmer House in Chicago, Oct. 14-19, 1956.

This charity organization is unique in that it requests no funds, merely discarded eyeglasses and metal bits, the salvage of which is sold and the funds used to defray the costs of new prescription glasses and artificial eyes.

SOCIETY NEWS

Canadian Ophthalmological Society.—At the recent Nineteenth Annual Meeting of the Canadian Ophthalmological Society the following officers were elected: President: Dr. John McLean, Vancouver, B. C.; Vice-President: Dr. J. V. V. Nicholls, Montreal; Secretary: Dr. R. G. C. Kelly, Toronto, Ont.; Treasurer: Dr. Benjamin Alexander, Montreal; Editor-in-Chief of the Transactions: Dr. Clement McCulloch, Toronto, Ont.

New York Society for Clinical Ophthalmology.—The newly elected officers of the New York Society for Clinical Ophthalmology for the 1956-1957 season are the following: President: Max Chamlin; Vice-President: Harvey E. Thorpe; Recording Secretary: Jesse M. Levitt; Corresponding Secretary: Leon H. Ehrlich; Treasurer: Henry M. Kera; Historian: Robert S. Coles.

Committee Chairmen: Program: Abraham Schlossman; Instructive Session: Arthur Linksz; Legislative: Benjamin C. Rosenthal; Membership: Howard Agatston; Industrial: Edward M. Douglas.

American Ophthalmological Society.—At its annual meeting the American Ophthalmological Society elected the following officers for the current year: President: Dr. Frederick C. Cordes, San Francisco; Vice-President: Dr. Walter S. Atkinson, Watertown, N. Y.; Secretary-Treasurer: Dr. Maynard C. Wheeler, New York; Editor: Dr. Gordon M. Bruce, New York.

PERSONAL

Dr. Lorenz E. Zimmerman.—Dr. Lorenz E. Zimmerman, Chief, Ophthalmic Pathology Section of the Armed Forces Institute of Pathology, and an Associate Member of the District Medical Society, served as an instructor in pathology of the eye at the Lancaster Courses in Ophthalmology, Colby College, Waterville, Maine, July 9-21.

Dr. Zimmerman lectured on inflammation, granulomatous lesions of the eye, intraocular neoplasms, pathology of the optic nerve, and ocular trauma.

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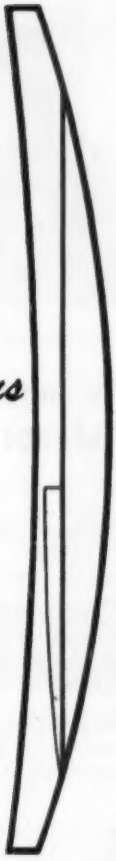

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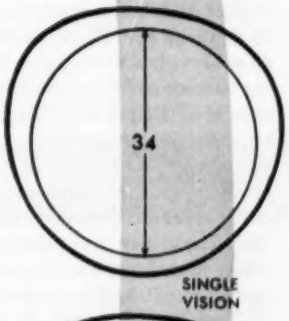

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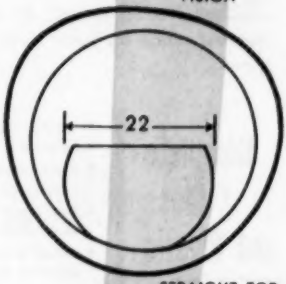

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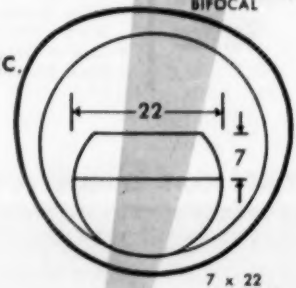

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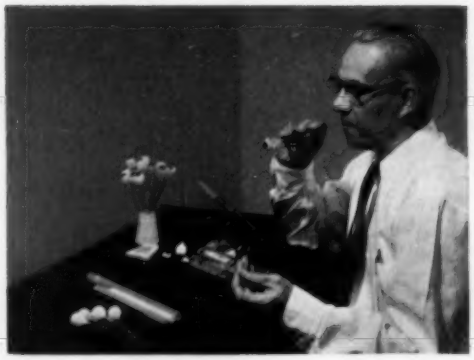

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Telegraph collect if specimen being sent.

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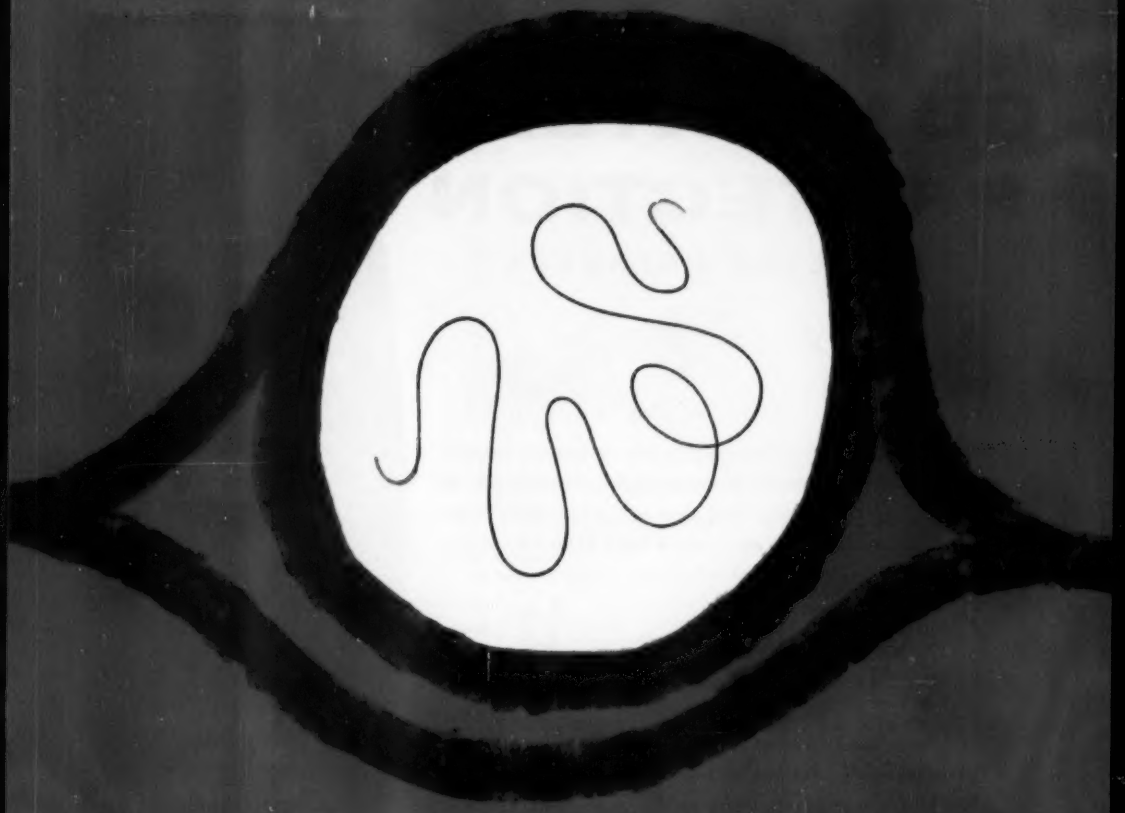

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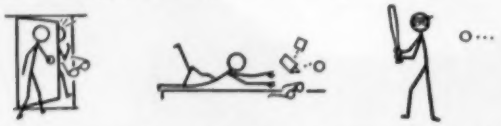

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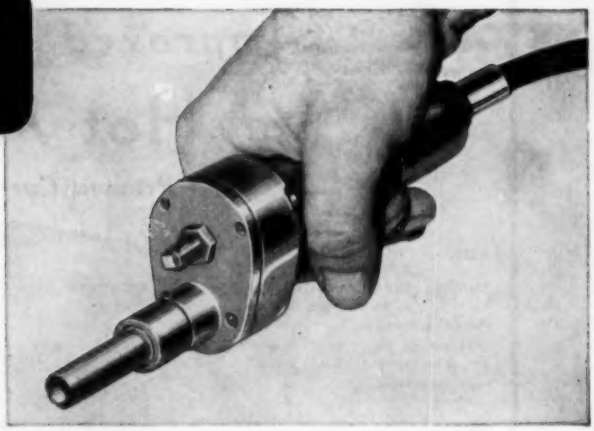

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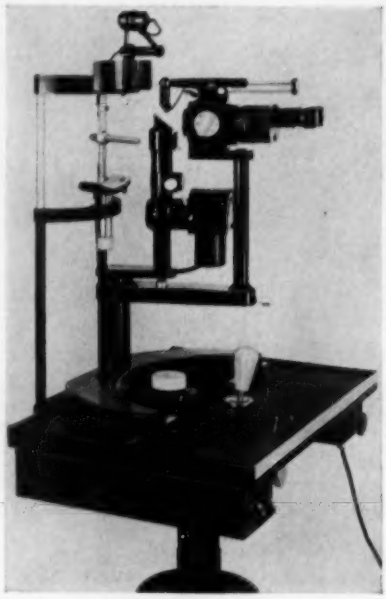

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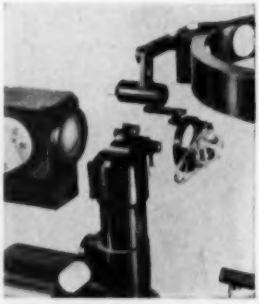

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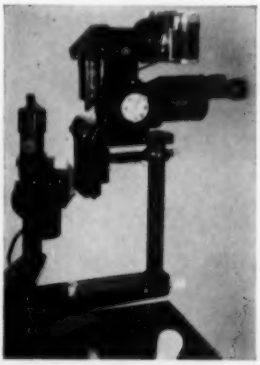

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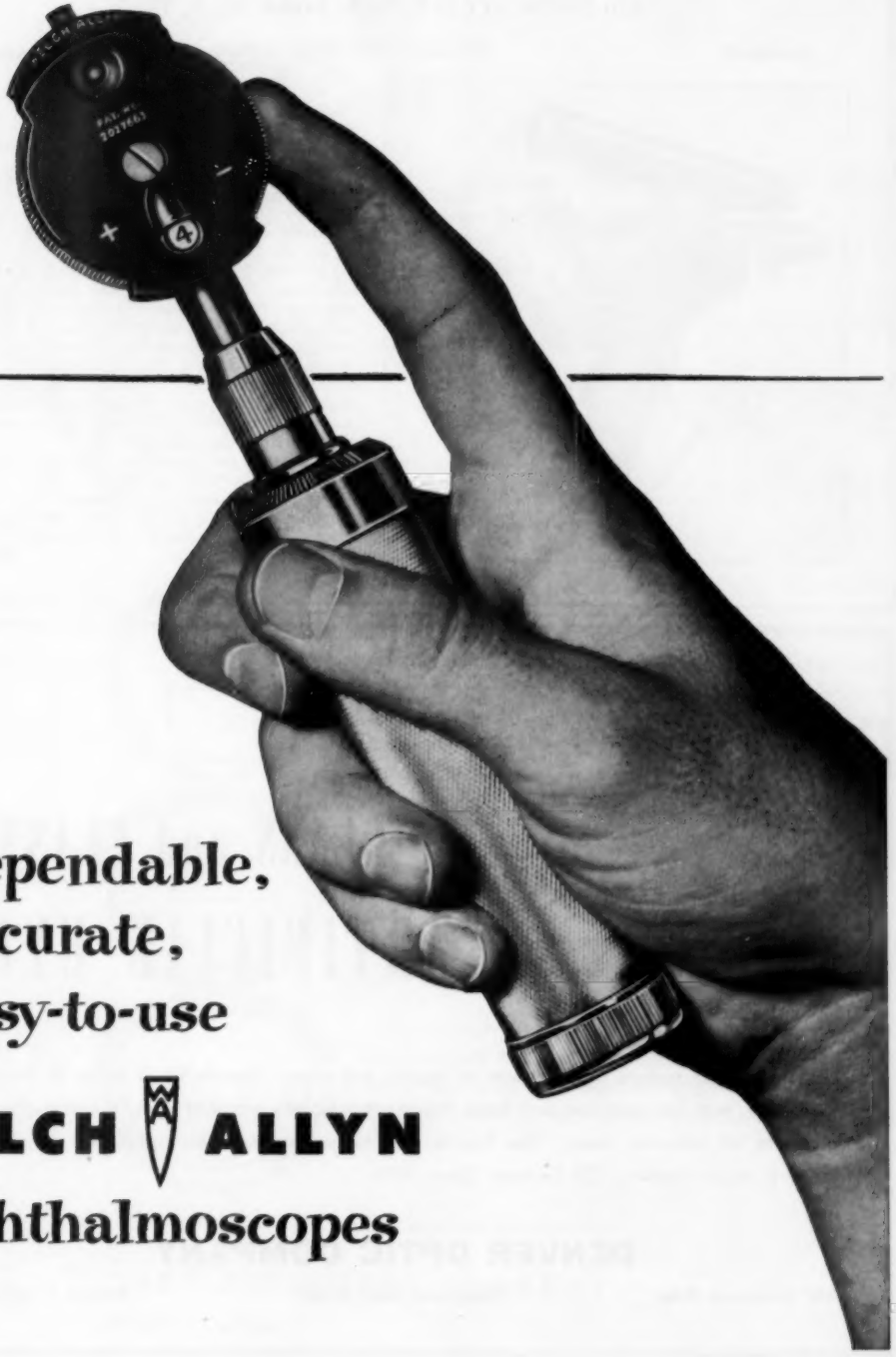

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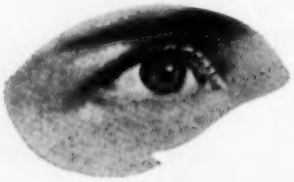

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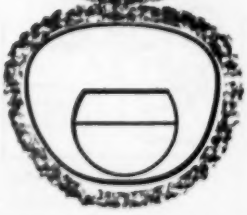

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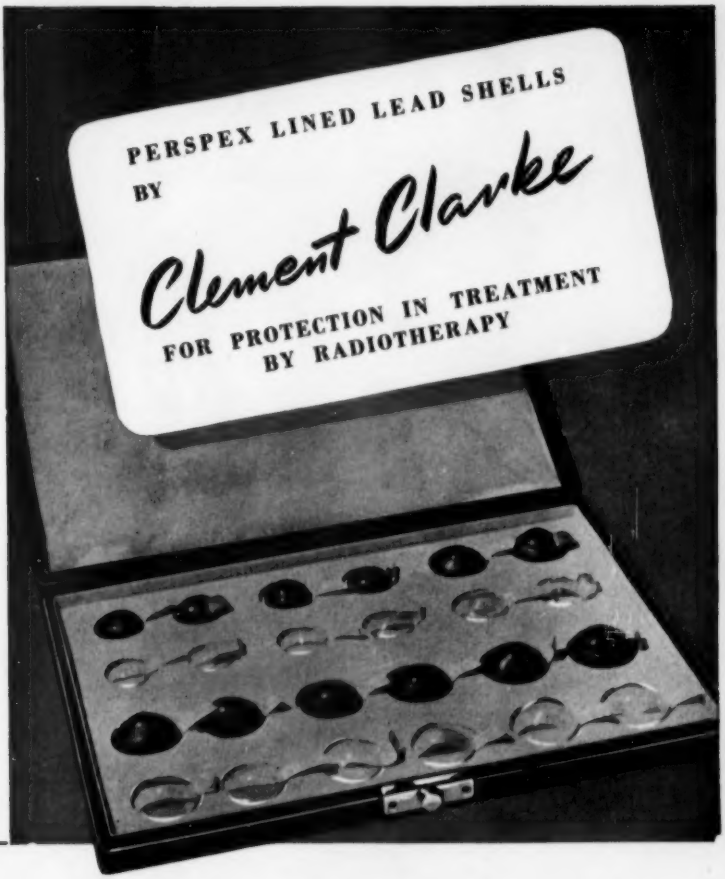

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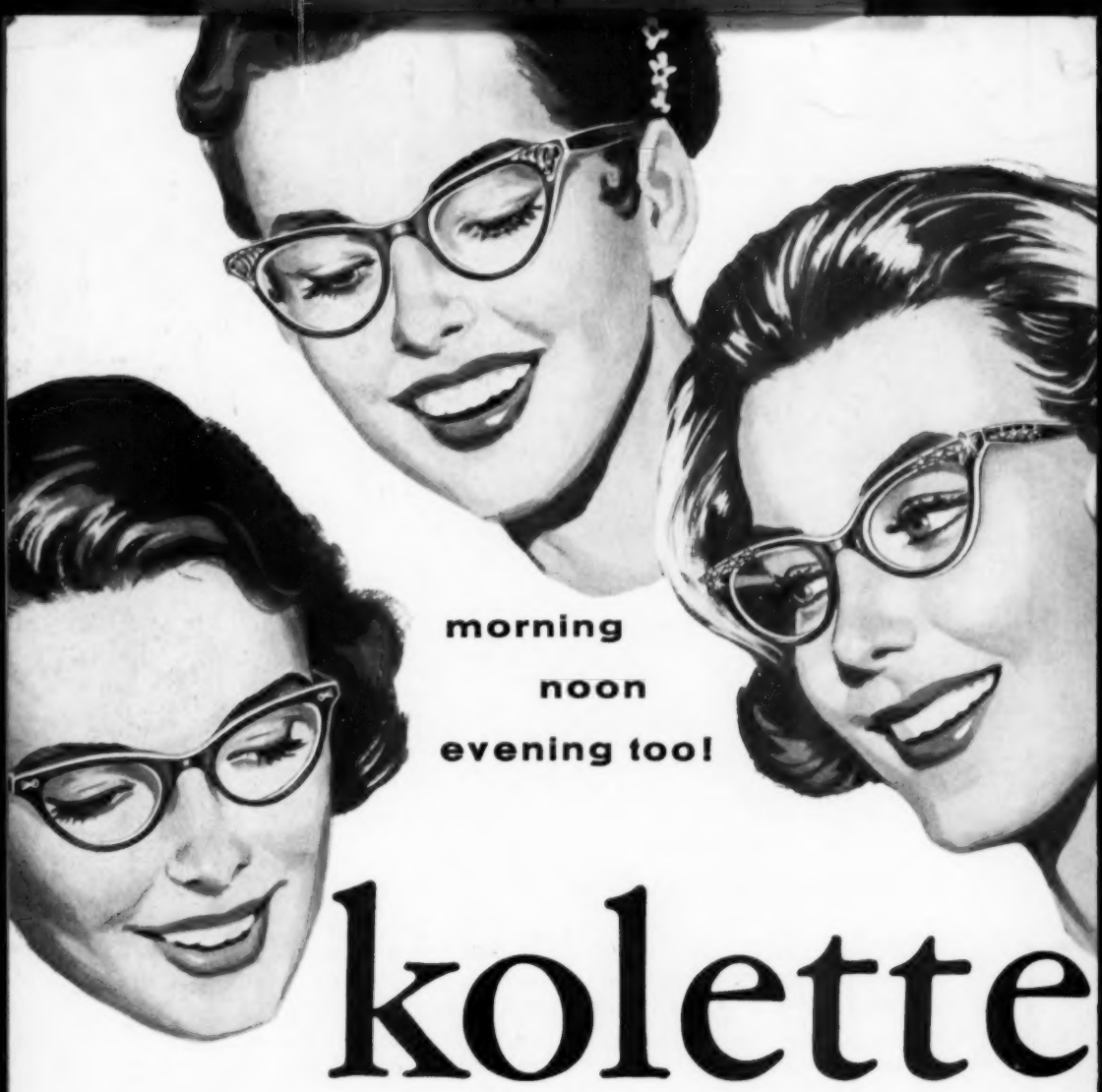

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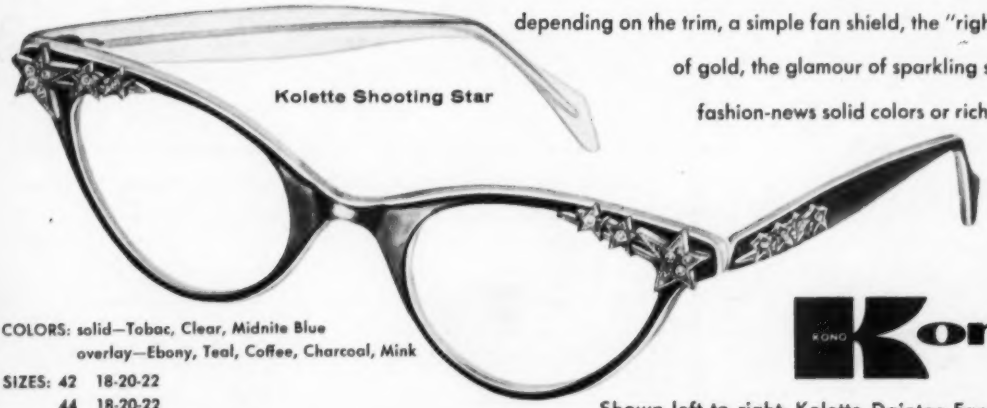

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